Cerebrovascular Disease Pathology and Parkinsonian Signs in Old Age

Aron S. Buchman, MD; Sue E. Leurgans, PhD; Sukriti Nag, MD, PhD; David A. Bennett, MD; Julie A. Schneider, MD, MS

Background and Purpose—Mild motor symptoms including parkinsonian signs are common in old age, but their underlying neuropathology is unclear. We tested the hypothesis that cerebrovascular pathologies are related to parkinsonian signs.

Methods—We studied brain autopsies from 418 deceased participants from the Religious Order Study, who underwent evaluation of parkinsonian signs with a modified version of the motor section of the Unified Parkinson’s Disease Rating Scale. Brains were evaluated for macroscopic and microinfarcts and the severity of arteriolosclerosis. Regression analyses were used to examine the association of cerebrovascular pathologies with parkinsonian signs.

Results—More than 35% of cases (N=149) showed macroscopic infarcts. Almost 30% of cases without macroscopic infarcts showed pathologies not detected by conventional brain imaging: microinfarcts (N=33 [7.9%]), arteriolosclerosis (N=62 [14.8%]), or both (N=24 [5.7%]). Macroscopic infarcts, specifically multiple cortical and ≥1 subcortical macroscopic infarcts, were related to higher global parkinsonian scores. The presence of multiple and cortical microinfarcts was associated with global parkinsonian score. Arteriolosclerosis was associated with global parkinsonian score, but this effect was attenuated and no longer significant after accounting for infarcts. Each of the 3 pathologies was separately associated with parkinsonian gait (macroscopic infarcts [estimate, 0.552; SE, 0.210; P=0.009]; microinfarcts [estimate, 0.424; SE, 0.213; P=0.047]; arteriolosclerosis [estimate, 0.191; SE, 0.056; P<0.001]). Further analyses showed that subcortical macroscopic and microinfarcts were specifically associated with the severity of parkinsonian gait.

Conclusions—Cerebrovascular pathologies, including macroscopic infarcts, microinfarcts, and arteriolosclerosis, are common in older persons and may be unrecognized common etiologies of mild parkinsonian signs, especially parkinsonian gait, in old age. (Stroke. 2011;42:3183-3189.)

Key Words: arteriolosclerosis ■ macroscopic infarcts ■ microinfarcts ■ parkinsonian signs

Cerebrovascular pathologies are commonly observed in the brains of older persons and clinical risk factors for vascular disease in older persons have been reported to be associated with an increased risk of having parkinsonian signs.7 Furthermore, brain imaging studies in older persons suggest a link between subclinical cerebrovascular disease and mild parkinsonian signs, including gait dysfunction in older persons.8–10 Although brain imaging is a sensitive tool for detecting macroscopic infarcts and white matter changes, microinfarcts and arteriolosclerosis cannot be directly visualized with routine imaging techniques and thus their link to parkinsonian signs in older persons is unknown. Postmortem studies provide a mechanism to document a wide range of cerebrovascular pathologies and to examine their association with parkinsonian signs in older persons in ways that complement clinical–radiological studies.
We used clinical and autopsy data from 418 community-dwelling older persons participating in the Rush Religious Order Study, a longitudinal clinical–pathological study of aging, to examine whether cerebrovascular pathologies, including macroscopic and microscopic infarcts and small vessel disease based on the severity of arteriolosclerosis, are related to parkinsonian signs in older persons.

Methods

Subjects
All subjects were older persons without known dementia at the time of enrollment participating in the Rush Religious Order Study.11 Each subject signed an informed consent and an anatomic gift act for donation of the brain at the time of death. The study was approved by the Institutional Review Board of Rush University Medical Center. More than 1100 persons without dementia agreed to participate and have completed their baseline clinical evaluation. The overall annual follow-up rate of survivors exceeds 95%, and the autopsy rate exceeds 90%. At the time of these analyses, completed postmortem data were available for the first 418 persons.

Clinical Evaluation and Diagnosis of Dementia
A uniform structured clinical evaluation was performed each year and includes medical history, neurological examination, and neuropsychological performance tests.12 At the time of death, all clinical data from all years were reviewed by a neurologist, blinded to all postmortem data, and a diagnostic opinion was rendered regarding dementia at the time of death.

Assessment of Parkinsonian Signs
Trained nurse clinicians administered a 26-item modified version of the motor portion of the United Parkinson’s Disease Rating Scale (Supplemental Methods; http://stroke.ahajournals.org).13,14 Four previously established parkinsonian sign scores were derived, including parkinsonian gait, bradykinesia, rigidity, and tremor. Each of the 4 parkinsonian sign scores had positively skewed distributions. The parkinsonian sign scores had positively skewed distributions. The parkinsonian sign score and gait score were subjected to regression analyses to compare global parkinsonian sign score in all analyses. Bradykinesia, rigidity, and tremor were relatively infrequent and so were treated as present or absent in analyses. We used regression analyses to compare global parkinsonian sign score and each of the 4 parkinsonian signs with demographic variables.

Postmortem Evaluation
The average postmortem interval was 8.3 hours (SD, 8.24 hours). Brains were removed, weighed, and brain regions that were not designated for freezing were immersion-fixed in 4% paraformaldehyde for a minimum of 72 hours. A uniform gross and microscopic neuropathologic examination was conducted as previously described.11

Macroscopic Cerebral Infarcts
We reviewed 1-cm slabs and recorded the age, volume (in millimeters cubed), side, and location of all cerebral infarcts visible to the naked eye as previously reported.11 Hemorrhagic infarcts were included in analyses. There was no minimum size required for macroscopic infarcts. All grossly visualized and suspected macroscopic infarcts were microscopically reviewed for histological confirmation. Infarct age (acute, subacute, and chronic) was estimated by the Institutional Review Board of Rush University Medical Center. More than 1100 persons without dementia agreed to participate and have completed their baseline clinical evaluation. The overall annual follow-up rate of survivors exceeds 95%, and the autopsy rate exceeds 90%. At the time of these analyses, completed postmortem data were available for the first 418 persons.

Microscopic Cerebral Infarcts
In all cases, the following regions were also dissected, processed, and embedded for diagnostic review: middle frontal cortex middle temporal cortex, anterior cingulate cortex, inferior parietal cortex, entorhinal cortex, hippocampus, anterior basal ganglia, anterior thalamus, and hemisection of the midbrain, including substantia nigra. Hematoxylin and eosin-stained 6-μm sections were used to identify microscopic infarcts as shown in Figure 1. Microscopic infarcts were defined as any infarct seen by microscopic examination but not identified by gross inspection. Microscopic infarcts ranged from cavitated to puckered to incomplete in appearance. All microscopic infarcts exhibited acellularity with varying degrees of gliosis and remaining macrophages. Any chronic microinfarct visualized microscopically by the neuropathologist was included in our analyses. Cases that were ambiguous were confirmed histologically and reviewed by a second neuropathologist and a consensus was used. Each microscopic infarct was recorded for age and location.15

Arteriolosclerosis
We used the term arteriolosclerosis to describe the histological changes commonly found in the small vessels of the brain in aging. Histological changes include intimal deterioration, smooth muscle degeneration, and fibrohyalinotic thickening of arterioles with consequent narrowing of the vascular lumen and are illustrated in Figure 2.16 Lipohyalinosis is sometimes used to describe this change but was originally used to describe vessels that had first undergone fibrinoid change. Because there are no standard guidelines to grade severity of arteriolosclerosis (or lipohyalinosis), we evaluated the vessels of the anterior basal ganglia with a semiquantitative grading system from 0 (none) to 6 (severe).17

Statistical Analysis
Parkinsonian Sign Scores
The parkinsonian sign scores had positively skewed distributions. The global parkinsonian sign score and gait score were subjected to a square root transformation, and the transformed scores were used in all analyses. Bradykinesia, rigidity, and tremor were relatively infrequent and so were treated as present or absent in analyses. We used regression analyses to compare global parkinsonian sign score and each of the 4 parkinsonian signs with demographic variables.

Brain Infarctions
In primary analyses, each case was classified according to whether any macroscopic infarcts were present. We created additional variables for secondary analyses. For quantity, we created a predictor with 3 levels: no (reference level), 1, and multiple macroscopic infarcts as previously described and a predictor with 4 levels.11 For location, we created 2 variables: cortical (presence of any macroscopic infarcts in any cortical region: reference, no cortical macroscopic infarcts) and subcortical macroscopic infarcts (presence of
any macroscopic infarcts in any subcortical region; reference, no subcortical macroscopic infarcts). To investigate quantity and location simultaneously, we created 4 variables: 1 and multiple cortical macroscopic infarcts (compared with persons with no cortical macroscopic infarcts) and 1 and multiple subcortical macroscopic infarcts (compared with no subcortical macroscopic infarcts). A similar approach was used for analyzing microinfarcts. Because the interval between last clinical examination and death in this group was on average 10.8 months (SD, 11.29), and perimortem infarcts (acute and subacute) would be unlikely to be related to clinical characteristics 11 months earlier, only chronic infarcts (estimated at being >3 to 6 months in age) were included in the primary analyses. The associations among cerebrovascular pathologies were examined with OR and \( \chi^2 \) tests.

**Association of Cerebrovascular Pathologies and Parkinsonian Signs**

We used a series of regression models to document the association of postmortem indices of cerebrovascular disease with global parkinsonian score proximate to death. All analyses controlled for age, sex, education, and postmortem evidence of PD defined as moderate or severe nigral neuronal loss with Lewy bodies (N = 36 [8.6%]). We then added additional terms for several potential confounding variables to examine their influence on the association of cerebrovascular pathologies and global parkinsonian score. We included both linear and nonlinear (quadratic) terms for body mass index because both low and high values may adversely affect neuropathology and parkinsonian signs. We repeated our analyses excluding cases with PD as well as including both acute and subacute infarctions. Next, we added an interaction term to examine whether the association of cerebrovascular pathologies and global parkinsonian sign score were modified by the presence of dementia. This model explicitly tests whether the associations between measures of cerebrovascular disease and parkinsonian signs differ among persons with and without dementia. In further analyses, we examined the association of cerebrovascular pathologies with each of the 4 individual parkinsonian signs. We used linear regression models to examine parkinsonian gait, Tobit regressions for bradykinesia, and logistic regressions for presence or absence of tremor and rigidity. Model assumptions of linearity, normality, independence of errors, and homoscedasticity of errors were examined graphically and analytically and were adequately met. All analyses were carried out using SAS/STAT software Version 9 (SAS Institute Inc, Cary, NC) on a Hewlett Packard ProLiant ML350 server running LINUX.18

### Results

**Summary of Parkinsonian Signs and Neuropathology Measures**

There were 418 participants (61.2% female) included in these analyses with a mean age at death of 88.5 years with a mean global parkinsonian sign score of 18.6 (14.77). Individual parkinsonian signs, chronic conditions, and postmortem indices are included in Table 1. Almost two thirds of cases showed evidence of \( \geq 1 \) indices of cerebrovascular pathology (1 measure N = 134 [32.1%]; 2 measures N = 89 [21.3%]; and 3 measures N = 45 [10.8%]). Macroscopic infarcts were observed in more than one third of cases and 110 cases (almost 75%) also had evidence of microinfarcts, arteriolar sclerosis, or both. There were almost 30% of cases (N = 119 [28.5%]) without evidence of macroscopic infarcts, which nonetheless showed evidence of microinfarcts, arteriolar sclerosis, or both. There were almost 30% of cases (N = 119 [28.5%]) without evidence of macroscopic infarcts, which nonetheless showed evidence of microinfarcts, arteriolar sclerosis, or both.

### Table 1. Clinical Characteristics and Cerebrovascular Disease Pathology of the Cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) or No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at death, y</td>
<td>88.5 (5.38)</td>
</tr>
<tr>
<td>Female sex</td>
<td>256 (61.2%)</td>
</tr>
<tr>
<td>White, non-Hispanic, no. (%)</td>
<td>403 (96.3%)</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.9 (3.14)</td>
</tr>
<tr>
<td>Last MMSE (maximum 30)</td>
<td>22.7 (8.86)</td>
</tr>
<tr>
<td>Dementia, no. (%)</td>
<td>188 (45%)</td>
</tr>
<tr>
<td>Depressive symptoms (maximum 10)</td>
<td>1.6 (1.91)</td>
</tr>
<tr>
<td>Global parkinsonian sign score (maximum 100)</td>
<td>18.6 (14.77)</td>
</tr>
<tr>
<td>Parkinsonian gait (maximum 100)</td>
<td>41.5 (23.49)</td>
</tr>
<tr>
<td>Rigidity (maximum 100)</td>
<td>11.7 (21.10)</td>
</tr>
<tr>
<td>Bradykinesia (maximum 100)</td>
<td>21.4 (20.37)</td>
</tr>
<tr>
<td>Tremor (maximum 100)</td>
<td>5.2 (11.67)</td>
</tr>
<tr>
<td>Summary of self-report medical conditions</td>
<td>1.7 (1.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>180 (43.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>159 (38.3%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>108 (25.8%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>102 (24.4%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>86 (20.6%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>39 (9.4%)</td>
</tr>
<tr>
<td>Head injury</td>
<td>31 (7.4%)</td>
</tr>
<tr>
<td>Cerebrovascular pathologies</td>
<td></td>
</tr>
<tr>
<td>Macroscopic infarcts</td>
<td>N = 150 (35.9%)</td>
</tr>
<tr>
<td>Location—cortical</td>
<td>48 (11.5%)</td>
</tr>
<tr>
<td>Location—subcortical</td>
<td>124 (29.7%)</td>
</tr>
<tr>
<td>No. per case (%)</td>
<td>1–78 (18.7%); 2–37 (8.9%); 3–18 (4.3%); 4–10 (2.4%); ( \geq 5–7 ) (1.7%)</td>
</tr>
<tr>
<td>N = 125 (29.9%)</td>
<td>53 (12.7%)</td>
</tr>
<tr>
<td>Location—cortical</td>
<td>79 (18.9%)</td>
</tr>
<tr>
<td>Location—subcortical</td>
<td></td>
</tr>
<tr>
<td>No. per case (%)</td>
<td>1–77 (18.4%); 2–30 (7.2%); 3–13 (3.1%); 4–4 (1.9%); ( \geq 5–1 ) (0.2%)</td>
</tr>
<tr>
<td>Arteriolosclerosis</td>
<td></td>
</tr>
<tr>
<td>None, possible, or minimal</td>
<td>245 (58.7%)</td>
</tr>
<tr>
<td>Mild</td>
<td>117 (28.0%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>43 (10.3%)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (3.1%)</td>
</tr>
</tbody>
</table>

MMSE indicates Mini Mental State Examination; SD, standard deviation.

### Macroinfarcts

Macroinfarcts were strongly related to both microinfarcts (OR, 3.12; SE, 0.69; \( P<0.001 \)) and arteriolosclerosis (OR, 2.4; SE, 0.62; \( P<0.001 \)). Arteriolosclerosis and microinfarcts were not related (OR, 1.32; SE, 0.33; \( P=0.319 \)).

### Association of Cerebrovascular Disease and Global Parkinsonian Score

All 3 cerebrovascular pathologies were related to global parkinsonian score in unadjusted analyses (macroscopic infarcts \( \rho=0.21; P<0.001 \); microscopic infarcts \( \rho=0.12; P<0.034 \); arteriolosclerosis \( \rho=0.23; P<0.001 \)). Next, we
conducted a series of linear regression models to examine the relation of cerebrovascular pathologies with global parkinsonian sign scores before death controlling for age at time of death, sex, education, and postmortem evidence of PD. We also evaluated the effect of location and number of infarcts, which have been found to be important factors in other outcomes (eg, dementia).

Macroscopic infarcts were related to global parkinsonian sign scores before death (Table 2, Model A). In secondary analyses, we found that multiple macroscopic infarcts (estimate, 0.577; SE, 0.175; \( P = 0.001 \)) and in particular \( \geq 3 \) infarcts were related to global parkinsonism (estimate, 0.882; SE, 0.236; \( P < 0.001 \)). Both cortical (estimate, 0.421; SE, 0.206; \( P = 0.041 \)) and subcortical macroscopic infarcts (estimate, 0.391; SE, 0.146; \( P = 0.008 \)) showed separate associations with a higher global parkinsonian score. In further analyses, multiple cortical (estimate, 1.054; SE, 0.337; \( P = 0.002 \)) or a single subcortical macroscopic infarcts (estimate, 0.413; SE, 0.174; \( P = 0.018 \)) were related to a higher global parkinsonian score.

Microinfarcts showed a trend for an association with global parkinsonian sign scores (results not shown). In secondary analyses that controlled for macroscopic infarcts, multiple microscopic infarcts (estimate, 0.460; SE, 0.208; \( P = 0.027 \)) and in particular \( \geq 3 \) were associated with higher global parkinsonism (estimate, 1.090; SE, 0.318; \( P < 0.001 \)). Cortical but not subcortical microinfarcts were associated with a higher global parkinsonian score (estimate, 0.401; SE, 0.193; \( P = 0.039 \)). In further analyses, in particular multiple cortical microinfarcts (estimate, 0.460; SE, 0.208; \( P = 0.027 \)) were related to a higher global parkinsonian score.

Arteriolosclerosis was associated with global parkinsonian score (Table 2, Model C), but the effect was attenuated and no longer significant in the final model including all 3 cerebrovascular pathologies (Table 3).

Other conditions might affect parkinsonian signs and confound the associations of macroscopic infarcts and parkinsonian signs. We repeated the core models at the same time as adding terms for potential confounding variables. The estimates for the associations of cerebrovascular pathologies and global parkinsonian scores were unchanged when we included terms for body mass index, depressive symptoms as well 7 chronic conditions listed in Table 1 in a single model (Table 2).

Because both infarcts and parkinsonian signs are associated with an increased risk of dementia, we investigated

Table 3. Cerebrovascular Disease Pathology and Parkinsonism*

<table>
<thead>
<tr>
<th>Pathology Measure</th>
<th>*Global Parkinsonian ( \beta ) (SE, ( \hat{\beta} ))</th>
<th>*Parkinsonian Gait ( \beta ) (SE, ( \hat{\beta} ))</th>
<th>( \hat{\beta} ) Rigidity ( \beta ) (SE, ( \hat{\beta} ))</th>
<th>( \hat{\beta} ) Bradykinesia ( \beta ) (SE, ( \hat{\beta} ))</th>
<th>( \hat{\beta} ) Tremor ( \beta ) (SE, ( \hat{\beta} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic infarcts</td>
<td>0.359 (0.144, 0.013)</td>
<td>0.552 (0.210, 0.009)</td>
<td>0.853 (0.256, &lt;0.001)</td>
<td>0.420 (0.185, 0.223)</td>
<td>-0.212 (0.227, 0.351)</td>
</tr>
<tr>
<td>Microscopic infarcts</td>
<td>0.149 (0.146, 0.308)</td>
<td>0.424 (0.213, 0.047)</td>
<td>0.031 (0.251, 0.902)</td>
<td>-0.007 (0.190, 0.972)</td>
<td>-0.196 (0.230, 0.293)</td>
</tr>
<tr>
<td>Arteriolosclerosis</td>
<td>0.055 (0.038, 0.150)</td>
<td>0.191 (0.056, &lt;0.001)</td>
<td>0.081 (0.0064, 0.052)</td>
<td>0.014 (0.493, 0.774)</td>
<td>-0.003 (0.060, 0.964)</td>
</tr>
</tbody>
</table>

SE indicates standard error.

*Based on regression model which included terms for age, sex, education, and postmortem evidence of Parkinson disease.

†Based on logistic regression model of presence or absence of parkinsonian sign, which included terms for age, sex, education, and postmortem evidence of Parkinson disease.

‡Based on Tobit model which included terms for age, sex, education, and postmortem evidence of Parkinson disease.
whether the relationship between infarcts and global parkinsonian sign score might vary with dementia by adding an interaction term to the core model (Table 2, Model A). Although global parkinsonian sign score was higher in participants with dementia, the association of macroscopic infarcts and global parkinsonian sign scores did not vary between persons with and without dementia (estimate, 0.109; SE, 0.253; \( P = 0.666 \)).

In further analyses we found that the associations of cerebrovascular pathologies and global parkinsonism (Table 2) were unchanged when we excluded cases with postmortem evidence of PD (Table 2) as well as when we used continuous measures for the frequencies of chronic macroscopic and microscopic infarcts (results not shown). Moreover, when we included the total number of all infarcts including acute, subacute, and chronic infarctions, the results were attenuated but still significant (results not shown).

**Association of Cerebrovascular Disease and the Individual Parkinsonian Signs**

The global parkinsonian sign score is a summary of the 4 individual parkinsonian signs. In further analyses, we examined whether cerebrovascular pathologies were related to the individual parkinsonian signs. The presence of macroscopic infarcts was associated with parkinsonian gait and rigidity but not with bradykinesia or tremor before death (Table 3). The presence of subcortical (estimate, 0.827; SE, 0.218; \( P < 0.001 \)) but not cortical macroscopic infarcts (estimate, 0.315; SE, 0.307; \( P = 0.306 \)) was associated with a higher level of gait impairment. This association was observed for both single (estimate, 0.797; SE, 0.262; \( P = 0.003 \)) and multiple (estimate, 0.892; SE, 0.304; \( P = 0.004 \)) subcortical macroscopic infarcts. Microinfarcts were also associated with parkinsonian gait even after controlling for macroscopic infarcts (Table 3). In further analyses, we found that it was multiple subcortical microinfarcts (estimate, 0.888; SE, 0.307; \( P = 0.004 \)) rather than cortical microinfarcts, which were related to an increased parkinsonian gait score. Athereosclerosis had a separate effect on parkinsonian gait after controlling for both macroscopic and microinfarcts (Table 3). These associations did not vary between those with and without dementia (results not shown).

**Discussion**

In this clinical–autopsy study of \( > 400 \) community-dwelling older persons, we found that cerebrovascular pathologies, including macroscopic and microinfarcts as well as small vessel disease, based on the severity of arteriolosclerosis were present in almost two thirds of cases. Furthermore, almost 30% of cases without macroscopic infarcts showed pathologies not likely to be directly detected by conventional brain imaging, including microinfarcts, arteriolosclerosis, or both. Each of the 3 cerebrovascular pathologies was separately associated with the severity of parkinsonian signs, especially parkinsonian gait. Subcortical macroscopic infarcts, subcortical microinfarcts, and arteriolosclerosis appear to be particularly important in the parkinsonian gait impairment. Together these data suggest that a substantial portion of older people have brain tissue damage and small vessel disease that are unlikely to be detected before death and suggest that cerebrovascular disease may be an even larger public health challenge than currently estimated. Furthermore, cerebrovascular pathologies in older persons may contribute to the development of what is currently considered “normal” age-related motor symptoms such as parkinsonian signs.

There are currently approximately 40 million persons aged \( > 65 \) years in the United States and by 2030, \( > 70 \) million persons, approximately 1 in 5 Americans, will be aged \( > 65 \) years.\(^{19} \) Loss of motor function is a familiar consequence of aging, but the specific motor abilities impaired in old age vary and encompass a wide spectrum, including reduced gait speed and loss of muscle strength and bulk, balance, and dexterity. Mild parkinsonian signs is 1 of the constructs that has been used to assess mild motor symptoms in older persons and these signs have been shown to be related to adverse health consequences, including death, disability, and dementia.\(^{1–4,20} \)

Although parkinsonian signs in old age are common and may affect up to 50% or more of community-dwelling older persons by aged 85 years,\(^{4} \) little is known about their underlying neuropathology. Because the combination of both Lewy bodies and nigral degeneration, the pathognomonic feature of PD, are relatively uncommon in the aging brain, they cannot account for the common occurrence of parkinsonian signs reported in older persons. To investigate the possible role of extranigral factors, after accounting for PD pathology, the current study focused on cerebrovascular pathologies, which are common in the aging brain and have been studied in vascular parkinsonism.\(^{21–23} \)

The term arteriosclerotic parkinsonism was first used by Critchley\(^{24} \) and no clear consensus has been developed that allows clinical differentiation of the neurodegenerative disorder PD from cases caused by severe vascular disease.\(^{21–23} \) In contrast to the mild parkinsonian signs studied in the current study, the clinical parkinsonian signs in vascular parkinsonism are much more severe, which underscores why these individuals may receive a clinical diagnosis of PD.\(^{25,26} \) Both postmortem and brain imaging studies have been used in vascular parkinsonism to demonstrate the presence of underlying cerebrovascular pathologies as well as the absence of postmortem evidence of PD.\(^{21–23} \) In contrast, we are not aware of any autopsy studies and there are few brain imaging studies that have explored the role of cerebrovascular pathologies and mild parkinsonian signs in old age.\(^{9,10} \) Similar to cognition, structural brain imaging may provide a window to both direct and surrogate markers of currently undetectable vascular pathologies, which may contribute to mild parkinsonian signs in old age. For instance, in a recent imaging–pathology study, microscopic infarcts were not only related to macroscopic infarcts, but also to leukoencephalopathy.\(^{27} \) Indeed, 2 recent brain imaging studies showed that there was a robust association among the size of white matter hyperintensities, a presumed marker of vascular disease, and lacunar brain infarcts with mild parkinsonian signs in older persons, suggesting that cerebrovascular pathologies may play an important role in the development of parkinsonian signs.\(^{10} \) The current clinical–pathological study supports and extends prior imaging studies by providing direct and compelling evidence that cerebrovascular pathologies, including macro-
scopic and microscopic infarcts as well as the severity of small vessel arteriolosclerosis, contribute to the development of mild parkinsonian signs in old age.8,28,29

Cerebrovascular pathology appears to be particularly important in the severity of parkinsonian gait impairment and subcortical cerebrovascular pathology, including macroscopic infarct, microinfarcts, and arteriolosclerosis, appears to be the main culprit. We are not aware of previous studies demonstrating independent roles for microinfarcts and the severity of arteriolosclerosis in the development of parkinsonian gait. Given that microinfarcts and severity of arteriolosclerosis are not discernable during life, these pathologies likely represent unrecognized common etiologies for parkinsonian gait in older persons30 and support clinical–imaging studies that suggest subclinical cerebrovascular disease abnormalities are associated with gait dysfunction in older persons.8,31 These data have important translational implications. First, they raise the question as to whether improved public health strategies for the increased prevention and more aggressive treatment of vascular risk factors and diseases before death might decrease the burden of mild age-related parkinsonian signs. Second, because microinfarcts and arteriolosclerosis are not directly detected with conventional brain imaging and were observed in almost 30% of cases in this study, these data suggest that the contribution of cerebrovascular disease to loss of motor function in older age is likely underestimated. Indeed, the current study is among the first to show the clinical relevance of specifically subcortical microinfarcts as well as a deleterious effect of arteriolosclerosis separate from either macro- or microinfarcts. Third, because small vessel disease has a separate relationship with parkinsonian gait after accounting for both macroscopic and microscopic infarcts, one may hypothesize that there are either structural or functional brain tissue changes other than infarcts that are also contributing to parkinsonian signs. Indeed, the small vessel changes observed in the current study may be related to the white matter hyperintensities previously recognized with brain imaging studies and which correlated with parkinsonian signs.30 Further clinical–pathological–imaging studies will be needed to delineate antemortem imaging markers as well as the pathophysiology of both microinfarcts and small vessel disease in the development of motor impairment in old age.

This study has some limitations. Microinfarcts were measured in many regions classically related to cognitive function and arteriolosclerosis severity was estimated only in the anterior basal ganglia, which may underestimate the association with parkinsonian signs. Further study of microvascular pathology in additional brain regions is warranted. Brain imaging data were not obtained in this study and might provide a way to link postmortem findings to antemortem brain imaging. Finally, our findings are cross-sectional so causal inferences are limited. It is possible that the cerebrovascular pathologies do not play a causal role in the development of parkinsonian signs, but rather both cerebrovascular pathologies and parkinsonian signs might be caused by a third factor. There are also several strengths to the study, including the community-based cohort with large numbers of women and men with high rates of clinical follow-up and autopsy. Uniform structured clinical procedures were used that included a detailed assessment of parkinsonian signs used in other studies. Uniform structured postmortem procedures were used that assessed several cerebrovascular pathologies, which cannot be directly detected with current imaging techniques.

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None.

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METHODS

Assessment of Parkinsonian Signs

Trained nurse clinicians administered a 26-item modified version of the motor portion of the United Parkinson’s Disease Rating Scale (mUPDRS) as previously described.\textsuperscript{1,2} The modifications were minor and were intended to make the scale more applicable to persons without PD and easier for non-physicians to administer and score. Four previously established parkinsonian sign scores were derived from the 26 items assessed. Parkinsonian gait was based on 6 items: arising from a chair, shuffling gait, body bradykinesia, turning, posture, and postural stability. Bradykinesia was based on 8 items: right and left finger taps, fist clench, pronation-supination, and leg agility. Rigidity was based on 5 items, one each for neck and all four extremities. Tremor was based on 7 items: resting tremor of chin-jaw and all four extremities, and action-postural tremor of both hands. Each of the 26 items was rated on a 0-5 scale: 0=Normal; 1=Slowing OR reduction in amplitude which could be normal; 2=Mild slowing and reduction in amplitude; 3=Moderately impaired. Definite early fatiguing and may have occasional arrests in movement; 4=Severely impaired. Frequent hesitation in initiating movements; 5=Can barely perform the task.

The domain score was calculated by adding the number of points (0-5) assigned to each of the individual items which were rated e.g., 8 items for bradykinesia. The total number of points for these 8 items is the raw bradykinesia score. This score was then divided by the maximal possible score which could be given for the domain which in the case of bradykinesia is 40 (8x5=40). This percentage (actual points/maximal points) was then multiplied by 100. Thus, while the number of items varied for each of the 4 parkinsonian signs, each the four signs were scaled from 0 to 100. A summary global parkinsonian sign score, was constructed by averaging the four individual parkinsonian sign scores. These measures have high inter-rater reliability and short-term temporal stability and are reproducible in men and women in aging and dementia from a variety of cohorts.\textsuperscript{1,2}
References


高齢者における脳血管疾患病理とパーキンソン徴候
Cerebrovascular Disease Pathology and Parkinsonian Signs in Old Age

Aron S. Buchman, MD1,2; Sue E. Leurgans, PhD1,2; Sukriti Nag, MD, PhD1,3; David A. Bennett, MD1,2; Julie A. Schneider, MD, MS1,3

1 Rush Alzheimer's Disease Center, 2 Department of Neurological Sciences, and 3 Department of Pathology, Rush University Medical Center, Chicago, IL.

背景および目的: パーキンソン徴候を含む軽度の運動症状は高齢者によくみられるが、その根拠となる神経病理は明らかにされていない。本研究では、脳血管系病理がパーキンソン徴候と関連があるという仮説を検証した。

方法: Religious Order Study の死亡した被験者 418 例について脳の剖検所見を検討した。被験者は改変統一パーキンソン病評価尺度の運動機能項目に基づきパーキンソン徴候の評価を受けていた。脳は肉眼で認められた梗塞、微小梗塞、および細動脈硬化の重症度について評価された。脳血管系病理とパーキンソン徴候との関連は回帰分析により解析した。

結果: 肉眼で梗塞が認められた症例は 35%超 (149 例) であった。また、肉眼で梗塞が認められなかった症例の約 30%では、従来の脳画像検査では検出されない次の病理がみられた: 微小梗塞 [33 例 (7.9%)], 細動脈硬化 [62 例 (14.8%)], またはその両方 [24 例 (5.7%)]。肉眼で認められた梗塞は、特に多発性皮質梗塞および 1 箇所以上の肉眼的皮質下梗塞の場合、総合パーキンソンスコアが高かった。多発性の皮質微小梗塞の存在と総合パーキンソンスコアとの関連が認められた。細動脈硬化は総合パーキンソンスコアと関連していたが、この関連は弱く、梗塞について補正した後、有意性は認められなかった。これら 3 つの病理はそれぞれ独立してパーキンソン歩行と関連していた (肉眼で認められた梗塞 [推定値: 0.552, SE: 0.210, p = 0.009], 微小梗塞 [推定値: 0.424, SE: 0.213, p = 0.047], 細動脈硬化 [推定値: 0.191, SE: 0.056, p < 0.001])。さらに解析した結果、肉眼で認められた梗塞、微小梗塞、および細動脈硬化を含む脳血管系の病因病理は高齢者によくみられ、高齢者における軽度のパーキンソン徴候、特にパーキンソン歩行の重症度と関連していた。

結論: 肉眼で認められた梗塞、微小梗塞、および細動脈硬化を含む脳血管系の病因病理は高齢者によくみられ、高齢者における軽度のパーキンソン徴候、特にパーキンソン歩行の認識が低いかよくみられる病理である可能性が考えられる。

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表3 脳血管系病理とパーキンソン症候*

<table>
<thead>
<tr>
<th>病理所見</th>
<th>総合パーキンソンスコア</th>
<th>パーキンソン歩行</th>
<th>固縮</th>
<th>運動緩慢</th>
<th>振戦</th>
</tr>
</thead>
<tbody>
<tr>
<td>肉眼で認められた梗塞</td>
<td>0.359 (0.144, 0.013)</td>
<td>0.552 (0.210, 0.009)</td>
<td>0.853 (0.256, &lt;0.001)</td>
<td>0.420 (0.185, 0.223)</td>
<td>−0.212 (0.227, 0.351)</td>
</tr>
<tr>
<td>微小梗塞</td>
<td>0.149 (0.146, 0.308)</td>
<td>0.424 (0.213, 0.047)</td>
<td>0.031 (0.251, 0.902)</td>
<td>−0.007 (0.190, 0.972)</td>
<td>−0.196 (0.230, 0.293)</td>
</tr>
<tr>
<td>細動脈硬化</td>
<td>0.055 (0.038, 0.150)</td>
<td>0.191 (0.056, &lt;0.001)</td>
<td>0.081 (0.064, 0.052)</td>
<td>0.014 (0.493, 0.774)</td>
<td>−0.003 (0.060, 0.964)</td>
</tr>
</tbody>
</table>

*年齢、性別、学歴、およびパーキンソン病の剖検所見を含めた回帰モデルに基づく。

†年齢、性別、学歴、およびパーキンソン病の剖検所見を含めたパーキンソン徴候の有無に関するロジスティック回帰モデルに基づく。

‡年齢、性別、学歴、およびパーキンソン病の剖検所見を含めたトービット (Tobit) モデルに基づく。