Microvascular brain pathology and late-life motor impairment

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ABSTRACT

Objective: To test the hypothesis that microvascular brain pathology is associated with late-life motor impairment.

Methods: More than 2,500 persons participating in the Religious Orders Study or the Memory and Aging Project agreed to annual motor assessment and autopsy. Brains from 850 deceased participants were assessed for microvascular pathology including microinfarcts, cerebral amyloid angiopathy, and arteriolosclerosis, and we examined their association with global motor scores proximate to death.

Results: Mean age at death was 88.5 years. More than 60% of cases had evidence of 1 or more microvascular pathologies and of these more than half did not have observed macroinfarcts. In separate regression models adjusted for age, sex, and education, microinfarcts and arteriolosclerosis were associated with level of motor function proximate to death (arteriolosclerosis, estimate, -0.027 , SE 0.005 , $p < 0.001$; microinfarcts, estimate, -0.017 , SE 0.008 , $p = 0.026$). These associations were not attenuated when controlling for vascular risk factors and diseases, postmortem interval, or interval from last clinical examination, and did not vary with level of cognition or presence of dementia proximate to death. When the 3 microvascular pathologies, macroinfarcts, and atherosclerosis were considered together in a single model, more severe arteriolosclerosis (estimate, -0.021 , SE 0.005 , $p < 0.001$) and macroinfarcts (estimate, -0.019 , SE 0.006 , $p < 0.001$) showed separate effects with the level of motor function proximate to death.

Conclusions: Microvascular brain pathology is common in older adults and may represent an under-recognized, independent cause of late-life motor impairment. *Neurology*® 2013;80:712–718

GLOSSARY

AD = Alzheimer disease; **CAA** = cerebral amyloid angiopathy; **MAP** = Memory and Aging Project; **ROS** = Religious Orders Study.

As our population ages, the increasing burden of chronic motor impairments and disability is a growing public health challenge. Impaired motor function is a common consequence of aging and is present in 50% of adults by age 85 years.¹ Importantly, these impairments are progressive and associated with adverse health outcomes including mortality, falls, disability, and dementia,² but the pathologic basis for these impairments is unclear. Vascular disease is common with increasing age. Converging evidence suggests that small-vessel disease may be a systemic age-related disorder which affects many organs including heart, kidney, and retina.^{3–6} Similarly, even in the absence of stroke, brain imaging of older adults shows that lacunar infarcts as well as nonspecific white matter hyperintensities commonly thought of as surrogates for microvascular brain pathology are common in old age and associated with impaired cognition, gait, balance, falls, motor speed, and disability.^{7–12} While conventional brain imaging is an excellent tool for identifying many types of vascular pathologies, it cannot identify specific small-vessel diseases and the extent to which these pathologies are related to late-life motor impairments.^{7,13–15} To address these gaps in the literature, we used clinical and postmortem data from the first 850 decedents in the

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Religious Orders Study (ROS) and the Memory and Aging Project (MAP), clinical-pathologic cohort studies of chronic conditions of aging.^{16,17} We tested the hypothesis that microvascular brain pathology, including microinfarcts, cerebral amyloid angiopathy (CAA), and arteriolosclerosis, are associated with motor function proximate to death while controlling for macroinfarcts and atherosclerosis.

METHODS Subjects. Participants are from 2 ongoing studies of aging which employ common antemortem and postmortem data collection allowing analyses of data from the combined cohorts. At the time of these analyses, motor assessment proximate to death and completed postmortem data were available for 850 persons (ROS: 469; MAP: 381).^{16,17}

Assessment of motor function. A uniform structured clinical evaluation is performed each year that includes medical history, neurologic examination, and neuropsychological performance tests. Motor performances tested included grip and pinch strength, finger tapping, Purdue pegboard testing, gait (time and number of steps to walk 8 feet and turn 360°), and balance (time to stand on each leg and then on their toes for 10 seconds and the number of steps off line when walking an 8-foot line in a heel to toe manner).² These measures were scaled and averaged to obtain a summary global motor score. Composite measures of manual strength (2 tests), manual dexterity (2 tests), and gait (4 tests) were formed in a similar manner. We did not form a composite balance measure because the balance tests, unlike the other motor tests, were sometimes not attempted.

Postmortem brain assessment. The average postmortem interval was 8.40 hours (SD = 7.99 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 including postmortem indices of Alzheimer disease (AD) and Lewy body pathology was conducted as previously described.¹⁸

Microvascular pathology. Microscopic cerebral infarcts. In all cases, the following regions were dissected, processed, and embedded for review: middle frontal cortex, middle temporal cortex, anterior cingulate cortex, inferior parietal cortex, entorhinal cortex, hippocampus, anterior basal ganglia, anterior thalamus, and hemisection of midbrain including substantia nigra. Hematoxylin & eosin–stained 6- μ m sections were used to identify microscopic infarcts. Microscopic infarcts were defined as any infarct seen only by microscopic examination. Microscopic infarcts ranged from cavitated to a focal area of shrinkage due to astrogliosis associated with few remaining macrophages. Any chronic microinfarct visualized microscopically by the neuropathologist was included in our analyses. Cases that were ambiguous were reviewed by a second neuropathologist and a consensus was employed. Each microscopic infarct was recorded for age and location.¹⁹

Cerebral amyloid angiopathy. CAA pathology was assessed in 5 brain regions, including midfrontal, inferior temporal, angular gyrus, and calcarine cortices, and the hippocampus. Two or more blocks from each region were dissected from 1-cm-thick paraformaldehyde-fixed slabs, then paraffin-embedded, cut into 20- μ m sections, and mounted on glass slides. The presence of CAA was assessed in each region using immunohistochemical labeling with monoclonal antihuman-amyloid- β 1-16 (1:300, Elan Pharmaceuticals, San Francisco, CA). Positive controls were included in each run. CAA

pathology was measured in 5 brain regions using a 5-point scale (0–4) as previously described.²⁰

Cerebral arteriolosclerosis. Arteriolosclerosis describes the histologic changes commonly found in the deep penetrating small vessels of the brain in aging, including intimal deterioration, smooth muscle degeneration, and fibrohyaline thickening of arterioles, with consequent narrowing of the vascular lumen. There are no standard guidelines to grade severity of arteriolosclerosis. We evaluated the vessels of the anterior basal ganglia with a semiquantitative grading system from 0 (none) to 4 (severe) indicating more than twice the normal wall thickness as previously described.²¹

Other cerebrovascular pathologies. Macroscopic cerebral infarcts. We reviewed 1-cm slabs and recorded the age, volume (in mm³), side, and location of all cerebral infarcts visible to the naked eye as previously reported.¹⁸ 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 histologic confirmation. Infarct age (acute, subacute, and chronic) was estimated by gross histologic features and degree of cavitation.

Cerebral atherosclerosis. This describes the segmental or circumferential subintimal accumulation of lipid, plasma proteins, and calcium deposition (plaque) in the walls of large arteries. It was assessed on gross examination of the anterior, middle, and posterior cerebral arteries and their proximal branches at the circle of Willis using a semiquantitative scale of none (0) to severe (5) indicating near total or total involvement of all visualized arteries.

Statistical analysis. The associations among the microvascular pathologies were examined with Spearman correlations. In primary analyses, we used the total number of infarcts for each case. We created additional variables for secondary analyses. For quantity, we created a predictor with 3 levels: no (reference level), one, and multiple macroscopic infarcts, as previously described.¹⁸ For location, we created 2 variables: cortical (presence of any microscopic infarcts in any cortical region; reference = no cortical microscopic infarcts) and subcortical microscopic infarcts (presence of any microscopic infarcts in any subcortical region; reference = no subcortical microscopic infarcts). To investigate quantity and location simultaneously, we created 4 variables: one and multiple cortical microscopic infarcts (compared to persons with no cortical macroscopic infarcts), and one and multiple subcortical microscopic infarcts (compared to no subcortical microscopic infarcts). Since the interval between last clinical examination and death in this group was on average 8.90 months (SD = 10.31), and perimortem infarcts (acute and subacute) were not related to global motor scores recorded 9 months earlier (results not shown), only the total of chronic infarcts (estimated at being over 3–6 months in age) were included in the primary analyses. We used a series of regression models to document the association of postmortem indices of microvascular pathology with global motor score proximate to death. All analyses controlled for age, sex, and education. We then added additional terms for vascular risk factors and diseases to examine their influence on these associations. Next, we added an interaction term to examine whether the association of microvascular pathologies and global motor score varied with cognitive status or between the 2 cohorts. 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.²²

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review board of Rush University Medical Center. Written informed

consent and an anatomical gift act for brain donation at the time of death was obtained from all study participants.

RESULTS Summary of global motor score and cerebrovascular pathologies. Scores on the global motor score ranged from 0.24 to 1.41 (mean = 0.61; SD = 0.22) with higher scores indicating better motor performance. The clinical characteristics of cases included at their last visit before death and postmortem indices are included in table 1.

More than 60% (n = 508, 61.2%) of cases showed evidence of one or more indices of microinfarcts or moderate to severe microvascular pathology (1 measure n = 329, 39.6%; 2 measures n = 149, 18.0%; and all 3 measures n = 30, 3.6%). In more than 50% of the cases with microvascular pathology, macroinfarcts were not observed (n = 282, 55.5%). Additional details on the frequency and the severity of vascular pathologies are included in table 1.

Table 1 Characteristics of participants at last visit proximate to death (n = 850)

Measure	Mean ± SD or n (%)
Clinical characteristics at last visit	
Age at death, y	88.0 ± 6.58
Percentage of women	549 (64.6)
White non-Hispanic	808 (95.1)
Education, y	16.4 ± 3.56
Dementia	372 (43.8)
Unable to ambulate	129 (15.3)
Body mass index, m ² /kg	25.9 ± 5.30
Vascular risk factors and conditions	
Stroke history	193 (22.7)
Diabetes history	183 (21.6)
History of hypertension	508 (59.8)
Smoking (ever)	254 (29.9)
History of myocardial infarct	206 (24.2)
History of claudication	220 (25.9)
History of congestive heart failure	33 (13.2)
Postmortem cerebrovascular indices	
Macroscopic infarcts (chronic)	305 (35.9)
Cortical	104 (12.2)
Subcortical	240 (28.2)
Atherosclerosis (circle of Willis) (moderate-severe)	384 (45.4)
Microscopic infarcts (chronic)	240 (28.2)
Cortical	124 (14.6)
Subcortical	145 (17.1)
Cerebral amyloid angiopathy (moderate-severe)	153 (18.2)
Arteriolosclerosis (moderate-severe)	334 (39.8)

Microscopic infarcts were modestly associated with arteriolosclerosis ($r = 0.12$, $p < 0.001$) but showed only a trend with CAA ($r = 0.06$, $p = 0.08$) and arteriolosclerosis was modestly associated with CAA ($r = 0.09$, $p = 0.01$).

Association of microvascular pathology and global motor score. We conducted a series of linear regression models to examine the relation of microvascular pathologies with global motor scores prior to death controlling for age at time of death, sex, and education. The total number of microinfarcts was associated with the level of global motor score proximate to death (table 2, model A). The figure contrasts the level of global motor scores in individuals with and without microinfarcts. In further analyses multiple microinfarcts (estimate, -0.055 , SE 0.023, $p = 0.016$) rather than single microinfarcts were related to global motor score. There was a marginal association for subcortical microinfarcts and global motor score (estimate, -0.034 , SE 0.019, $p = 0.066$) but not cortical microinfarcts (results not shown).

The severity of arteriolosclerosis was strongly related to the level of global motor score proximate to death (table 2, model B). In contrast, CAA was not associated with the level of motor function proximate to death (table 2, model C). The figure contrasts global motor scores in individuals with moderate to severe arteriolosclerosis vs none or mild arteriolosclerosis.

Next, we included all 3 microvascular pathologies in a single model which controlled for demographics, macroinfarcts, and atherosclerosis. We used the adjusted R^2 to convey the magnitude of the association for the addition of postmortem indices to the core model with demographic variables alone. Together these vascular pathologies accounted for 4% of the R^2 of global motor score after considering demographic variables. Both arteriolosclerosis and macroinfarcts showed separate effects with the level of motor function proximate to death (table 2, model D). AD and Lewy body pathology have been reported to be associated with level of motor function in older adults.²³ In a final model, we added terms to model D to control for AD and Lewy body pathologies and the associations of arteriolosclerosis and macroinfarcts with global motor score were unchanged (results not shown).

The associations between microinfarcts and arteriolosclerosis and global motor score were not attenuated after controlling for vascular risk factors and diseases, postmortem interval, or interval from last clinical examination (results not shown). In further analyses, we added interaction terms to our core models, to examine if there was an interaction between microvascular pathology and the presence of dementia or the level of cognitive function proximate to death. The interaction terms were not significant (results not shown), suggesting that the association of microvascular pathology

Table 2 Microvascular pathology is related to global motor score proximate to death^a

Terms	Core model	Model A	Model B	Model C	Model D
Adjusted R ²	0.127	0.132	0.153	0.122	0.167
Microinfarcts		−0.017 (0.008, 0.026)			−0.005 (0.008, 0.510)
Arteriolosclerosis			−0.027 (0.005, <0.001)		−0.021 (0.005, <0.001)
Cerebral amyloid angiopathy				1.75E-7 (2.57E-7, 0.496)	1.87E-7 (2.51E-7, 0.478)
Macroinfarcts					−0.019 (0.006, <0.001)
Atherosclerosis					−0.006 (0.005, 0.178)

^a Based on a series of linear regression models examining level of global motor score proximate to death as a function of vascular pathologies. The core model shows the R² from the model which included terms for age, sex, and education alone without any measures of postmortem indices. Models A–C include a term for each type of microvascular pathology examined in the current study. Model D includes separate terms for macroinfarcts and atherosclerosis. Estimate (SE, *p* value). All models controlled for age, sex, and education.

and global motor score did not vary in cases with and without dementia or with the level of cognition proximate to death. In a final set of analyses we examined whether the association of microvascular pathology with global motor scores varied by cohort (MAP or ROS). There was not a significant interaction between cohorts and microinfarcts (estimate, 0.017; SE 0.015, *p* = 0.244) or arteriolosclerosis (estimate, 0.002; SE 0.011, *p* = 0.895), suggesting that the association between microvascular pathology and global motor scores was similar in both cohorts.

Associations of microvascular pathology with the components of global motor score. To see if microvascular pathology was more strongly associated with different components of the global motor score, we repeated the original analyses with several components of global motor score. In separate regression models, microinfarcts were associated with manual dexterity and gait, arteriolosclerosis was strongly associated with all the motor components, and CAA was not associated with these motor measures (table 3).

DISCUSSION In this clinical–autopsy study of 850 community-dwelling older persons, microvascular

pathology including microinfarcts, CAA, and arteriolosclerosis was common and observed in more than 60% of cases. Moreover, up to 35% had microvascular pathology alone without evidence of macroinfarcts. Not only were these pathologies common, but microinfarcts and arteriolosclerosis were associated with the severity of motor function proximate to death. When considered together in a single model, arteriolosclerosis and macroinfarcts showed independent effects with the level of global motor score proximate to death even when controlling for the other microvascular pathologies and atherosclerosis. Thus, many older adults have microvascular brain pathology that might not be detected prior to death. As a consequence, cerebrovascular disease may be an even larger public health challenge than currently estimated and the accumulation of microvascular pathology in the brains of older adults may represent an under-recognized cause of late-life motor impairments.

Impaired motor function in older adults is common, progressive, and associated with adverse health outcomes.^{1,2} A variety of non-neurologic diseases such as chronic pulmonary or heart disease as well as neurologic conditions including Parkinson disease, amyotrophic

Figure Microvascular pathology and motor function proximate to death

Box plot scores proximate to death.

Table 3 Microvascular pathology and components of global motor score^a

Microvascular pathology	Hand strength	Manual dexterity	Gait	Walking speed
Microinfarct	NS	−0.018 (0.006, 0.002)	−0.016 (0.007, 0.038)	NS
Arteriolosclerosis	−0.028 (0.006, <0.001)	−0.017 (0.004, <0.001)	−0.023 (0.005, <0.001)	−0.016 (0.004, <0.001)
Cerebral amyloid angiopathy	NS	NS	NS	NS

Abbreviation: NS = not significant.

^aBased on a series of linear regression models examining level of specific motor components of the global motor score proximate to death as a function of microvascular pathologies. Estimate (SE, *p* value). All models included terms for age, sex, and education, which are not shown.

lateral sclerosis, and cerebrovascular disease are well known to affect motor function. In contrast, motor deficits observed in older persons in the absence of overt diseases have been subsumed under several terms including sarcopenia,²⁴ physical frailty,²⁵ and parkinsonian signs.¹ While these motor deficits are widely known to be related to adverse health outcomes, their underlying mechanisms are unclear. For example, recent work has shown that declining strength in older adults is not accounted for by loss of skeletal muscle bulk alone.²⁶ On the other hand, others have reported both physiologic deficits in fully activating muscle as well as the accumulation of common neuropathologies in crucial motor-related brain regions of older adults without overt neurologic diseases, suggesting that neural factors may contribute to the development of late-life motor impairments.^{23,27,28} Brain imaging studies have also linked nonspecific white matter hyperintensities commonly thought of as surrogates for small vessel disease, with impaired gait, balance, falls, motor speed, and disability.^{7–12} Thus, like other organs, the accumulation of microvascular brain pathology may also contribute to late-life motor impairments in the absence of overt diseases.^{3–6} While extant brain imaging techniques may be very sensitive to the presence of white matter hyperintensities, complementary histopathologic studies are necessary to identify the specific types of small-vessel diseases affecting the brain.^{7,13–15}

The current clinical–histopathologic study provides important new data which complements extant brain imaging studies in several important ways. First, this study found that that one or more of 3 common microvascular pathologies including microinfarcts, CAA, or arteriolosclerosis are observed in more than 60% of older adults and up to 35% without evidence of microinfarcts. Second, the current study found that microvascular pathology, in particular arteriolosclerosis and microinfarcts, were associated with the severity of motor impairment proximate to death. Third, after controlling for the presence of microinfarcts, arteriolosclerosis was associated with level of motor function proximate to death. Together these data provide further support for an expanded conception of the role of cerebrovascular disease in older adults not only causing

devastating acute deficits from strokes, but a potentially larger role in late-life motor and cognitive impairments, as suggested by brain imaging studies.^{7–12} These findings underscore the importance of explicating the biology of small-vessel diseases in older adults as their treatment would provide a host of new targets for interventions to mitigate the growing burden of late-life motor impairment in our aging population.

While vascular pathologies examined in the current study were linked with motor function, the variance explained by the 5 postmortem indices which were examined accounted for only about 4% of global motor score as compared to 12% accounted for by demographic variables age, sex, and education. While this is a small effect size, it has important implications at the population level. While it is possible that more precise measures of pathology would improve the prediction, it is more likely that there are other pathologic processes which we did not measure in the current study which may make additional contributions to motor function such as brain imaging measures of white matter integrity, microbleeds, or measures of CNS inflammation. Moreover, motor function derives from integrated motor systems which are located in both the brain and in the spinal cord, as well as peripheral nerve and muscle. Thus, damage to brain or spinal cord or both can cause motor deficits. Thus, it is also possible that microvascular pathology may also affect motor networks which are located outside of the brain, such as in the spinal cord, and make independent contributions to late-life motor impairments. The current results add further support to the idea that the accumulation of common neuropathologies in older adults including vascular pathologies, synuclein, as well as AD pathology may contribute to the development of what is currently considered “normal” age-related motor and cognitive symptoms in persons without overt diseases. Further studies which examine the entire central motor pathway are needed to delineate the full contribution of accumulating neuropathologies to late-life motor impairments.

The study has strengths that lend confidence in the findings. All subjects were recruited from the

community and underwent an annual detailed clinical evaluation and on average were examined about 9 months proximate to death. Annual follow-up and autopsy rates were very high. Uniform, structured clinical and postmortem procedures were followed. All postmortem evaluations were performed by experienced and trained examiners blinded to all clinical data. The study also had limitations in that the cohort was selected and inferences regarding causality must be drawn with caution from observational studies. Further, the study did employ brain imaging of white matter integrity or neuronal, glial, or inflammatory changes in the brain that might cause both loss of motor function and microvascular pathologies in old age.

AUTHOR CONTRIBUTIONS

Dr. Buchman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He was involved with obtaining funding for the study, study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important

intellectual content. Dr. Yu provided statistical analyses and interpretation and critical revision of the manuscript for important intellectual content. Drs. Boyle, Levine, Nag, and Schneider were involved in study design, acquisition of data, and critically revised the manuscript for important intellectual content. Dr. Bennett was involved with obtaining funding, study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

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DISCLOSURE

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Comment: Microvascular disease and motoric dysfunction

Buchman et al.¹ report that the presence of microvascular disease (microinfarcts, cerebral amyloid angiopathy, and arteriolosclerosis) in brain autopsies done in 850 community-dwelling older adults was associated with motor impairments measured prior to death. These and other microvascular lesions such as cortical microbleeds are common in aging brains, but their clinical significance is not well-established.^{1,2} Some recent studies have linked microvascular lesions to risk of cognitive decline, but the relationship of this class of vascular lesions with various other geriatric syndromes is understudied. As with any retrospective study there are other role players (confounders, in epidemiology speak) that might explain the observed associations.¹ However, even after accounting for several major confounders, including vascular risk factors and disease, interval between the last examination and death, and presence of terminal cognitive impairment or dementia, the relationship with motor dysfunction survived.¹

These findings indicate an expanded clinical role for neurologists. Gait and motor examination is a standard part of the neurologic examination, used to identify gait patterns (such as parkinsonian or hemiparetic gaits) that help diagnose specific neurologic diseases.³ As the current study highlights, aging is also associated with motor function decline apart from those linked to specific neurologic diseases. Neurologists, as clinicians who often examine and investigate gait, have an opportunity to identify motoric decline (besides specific gait patterns) in a broader segment of the elderly population, and plan vascular investigations and interventions. As risk factors and biomarkers associated with individual microvascular lesions may vary, it would be important to identify specific lesions. However, standard neuroimaging procedures may not identify or distinguish among different microvascular lesions as can pathologic examination. Hence, translation of findings of this study to clinical practice will need development and implementation of new imaging techniques to reliably identify microvascular lesions in elderly patients as a prelude to preventive interventions.

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