Parkinsonian signs in subjects with mild cognitive impairment

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Abstract—*Background:* Parkinsonian signs such as gait disturbance, rigidity, bradykinesia, and tremor are common among individuals with dementia and are associated with negative outcomes, but little is known about parkinsonian signs among individuals with mild cognitive impairment (MCI). *Objective:* To examine the extent to which MCI is associated with parkinsonian signs and the relation between cognitive abilities and parkinsonism among individuals with MCI. *Methods:* Participants included 835 individuals from the Rush Memory and Aging Project, a clinical-pathologic study of common chronic conditions of old age. All participants underwent detailed clinical evaluations which included assessments of parkinsonian signs and cognitive function, and linear regression models were used to examine the associations of MCI and parkinsonism. *Results:* In a series of analyses controlled for age, sex, and education, individuals with MCI exhibited significantly more parkinsonism than individuals without cognitive impairment, particularly gait disturbance, bradykinesia, and rigidity. Among individuals with MCI, lower levels of cognitive function, particularly in perceptual speed, were associated with higher levels of parkinsonism; when classified according to MCI subtype, individuals with amnestic vs non-amnestic MCI differed from each other on only one parkinsonian sign, with non-amnestic MCI showing more gait disturbance. Because vascular factors can contribute to cognitive impairment and parkinsonian signs, the authors repeated the core analyses including terms for vascular risk factors and vascular disease and the associations between MCI and parkinsonism persisted. *Conclusions:* Mild cognitive impairment (MCI) is accompanied by parkinsonian signs, which are related to the severity and type of cognitive impairment. The association between MCI and parkinsonism is not explained by vascular risk factors or vascular disease.

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Parkinsonian signs such as gait disturbance, rigidity, bradykinesia, and tremor are common among older adults[1,2] and are associated with cognitive decline,[3] dementia,[3,4] and death.[1,5] These signs also are frequent among individuals with Alzheimer disease (AD)[6,7] and increase in severity as the disease progresses.[7] Increasing parkinsonism is strongly related to the rate of cognitive decline in AD,[8] and parkinsonism is also associated with mortality among individuals with AD.[9] Whereas parkinsonian signs once were considered a benign consequence of aging, it is now evident that parkinsonian signs are associated with morbidity and mortality in old age.

At present, little is known about parkinsonian signs among individuals with mild cognitive impairment (MCI), the transition state between normality and dementia.[10] Although the diagnosis of MCI is based on the presence of cognitive dysfunction in the absence of significant functional loss, individuals with MCI may actually be manifesting the earliest symptoms of dementia.[11,12] If this is the case, individuals with MCI likely have a broader range of symptoms, including parkinsonian signs, and these signs may be related to the cognitive profile of MCI. To our knowledge, only one study has examined parkinsonian signs in MCI[13]; findings indicated an association between amnestic MCI and parkinsonian signs, particularly rigidity.

We used data from the Rush Memory and Aging Project, a large longitudinal clinical-pathologic investigation of common chronic conditions of old age, to examine the associations between MCI and parkinsonian signs in more than 800 older adults free of dementia and PD. We sought to examine whether individuals with MCI are more likely than individuals without cognitive impairment to exhibit parkinsonian signs and, if so, whether these signs are associated with the severity and type of cognitive impairment among those with MCI.

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Methods. Participants were 835 individuals enrolled in the Rush Memory and Aging Project, an ongoing longitudinal clinical-pathologic study of common chronic conditions of old age.[14] Study

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Table 1 *Comparison of individuals without cognitive impairment vs MCI*

	No cognitive impairment, n = 598	Mild cognitive impairment, n = 237
Age, y	79.6 (6.8)	82.8 (6.9)
Education, y	14.5 (3.2)	14.3 (2.9)
Mini-Mental State Examination	28.4 (1.6)	26.4 (2.5)
Women, %	74.6	68.4
Non-Hispanic white, %	93.3	92.0

Values are mean (SD) or percent.

MCI = mild cognitive impairment.

participants are residents of approximately 40 senior housing facilities in the Chicago metropolitan area, including subsidized housing facilities, retirement communities, and retirement homes. Participation in the Rush Memory and Aging Project involves risk factor assessment, detailed annual clinical evaluations including medical history, neurologic and neuropsychological examinations, and organ donation at the time of death. The study was approved by the Institutional Review Board of Rush University Medical Center, and informed consent and an anatomic gift act were obtained from each participant following a detailed presentation of the risks and benefits associated with study participation.

At the time of these analyses, 901 participants had completed the baseline evaluation. Based on a previously described structured clinical evaluation,[15] all participants were classified by a physician with respect to dementia, Parkinson disease (PD), and other conditions. The diagnosis of dementia followed the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria,[16] which require a history of cognitive decline and evidence of impairment in at least two cognitive domains. The diagnosis of MCI was rendered for individuals who had cognitive impairment but who did not meet criteria for dementia, as previously described[14]; these criteria are identical to those used in research on MCI in the Religious Orders Study.[11,17] For specific analyses examining the subtypes of MCI, individuals who had MCI with relatively impaired episodic memory were considered amnestic MCI, whereas individuals who had MCI with relatively spared episodic memory were considered non-amnestic MCI, similar to the approach used in the Religious Orders Study.[18]

Because we were interested in examining parkinsonian signs among individuals who were free of dementia and PD at the baseline evaluation, 54 individuals with dementia, 9 with PD, 1 with dementia and PD, and 2 with missing data were excluded from these analyses. This resulted in a final group of 835 participants, including 237 with MCI and 598 without cognitive impairment. The mean age of the overall group was 80.5 years (SD = 6.7; range: 55 to 100), the mean education was 14.5 years (SD = 3.1; range: 1 to 28), and the mean score on the Mini-Mental State Examination (MMSE)[19] was 27.9 (SD = 2.1; range: 18 to 30). Demographic data for individuals with MCI and without cognitive impairment at baseline are presented in table 1; at baseline, individuals with MCI were older [$t(833) = 6.14$, $p < 0.001$] and had lower MMSE scores [$t(306) = -10.93$, $p < 0.001$].

Assessment of parkinsonian signs. A modified version[20,21] of the motor portion of the Unified PD Rating Scale[22] was used to quantify global parkinsonism and the specific parkinsonian signs in this cohort, as previously described.[23] The modifications were minimal and were intended to render the scale appropriate for individuals without PD and amenable to administration and scoring by non-physicians. Nurse clinicians administered the instrument to all participants after completing a structured training program, as previously described.[20] Four established parkinsonian signs were derived: gait disorder (based on six items), rigidity (based on five items), bradykinesia (based on four items), and tremor (based on two items); scores on the specific signs range from 0 to 100 and denote the percentage of the total possible score obtained. A global measure of parkinsonism was calculated by averaging the four sign scores. In previous research, these modified global and specific sign scores have been shown to have high inter-rater reliability and short-term temporal stability.[20]

Assessment of cognitive function. Cognitive function was assessed via a battery of 21 tests.[15] This battery included the MMSE,[19] but MMSE scores were used only to describe the cohort. Scores on 19 tests were used to create summary indices (see below) of the following five specific cognitive domains: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. Episodic memory was assessed via seven tests: immediate and delayed recall of story A from Logical Memory,[24] immediate and delayed recall of the East Boston Story,[25,26] Word List Memory, Word List Recall, and Word List Recognition[27]; semantic memory was assessed via three tests: a 15-item version of the Boston Naming Test,[27,28] Verbal Fluency,[26,27] and a 15-item reading test[26]; working memory was assessed via three tests: Digit Span Forward, Digit Span Backward,[24] and Digit Ordering[26,29]; perceptual speed was assessed via four tests: Symbol Digit Modalities Test,[30] Number Comparison,[26,31] and two indices from a modified version of the Stroop Neuropsychological Screening Test[32]; and visuospatial abilities were assessed via two tests: a 15-item version of Judgment of Line Orientation[33] and a 16-item version of Standard Progressive Matrices.[34] One additional test, Complex Ideational Material,[35] was used for diagnostic classification but was not used in the composite measure of cognition.

Summary scores for the five specific cognitive domains were derived by converting raw scores on each of the individual tests to z-scores, using the mean and SD of the entire cohort, and then averaging the z-scores from tests within a specific cognitive domain. A measure of global cognitive function was formed by averaging the z-scores of all 19 tests. Psychometric information on these summary scores, including factor analytic support for the five cognitive domains, is contained in previous publications.[15,36]

Assessment of vascular risk factors and vascular disease. Participants in the Rush Memory and Aging Project undergo a comprehensive medical history interview at the baseline evaluation, which includes numerous self-report questions pertaining to vascular risk factors (i.e., hypertension, diabetes mellitus, smoking) and vascular disease (i.e., heart attack, congestive heart failure, claudication, and stroke). In addition, medications are inspected and coded using the Medi-Span system,[37] as previously described.[38] For the purpose of this study, smoking history, heart attack, congestive heart failure, and claudication were rated as absent or present (0 or 1) as determined by self-report; hypertension and diabetes were rated as present if the participant reported having been diagnosed with the condition or was found to be on medication for the condition, and stroke was diagnosed based on self-report plus clinical examination, as previously described.[39] In order to directly assess the influence of cumulative vascular risk factor and vascular disease burden on parkinsonian signs in MCI, we computed summary scores indicating each individual's vascular risk factor sum (resulting in a score from 0 to 3 for each individual) and vascular disease sum (0 to 4). These summary scores were used in the analyses, in addition to the individual markers of vascular risk and vascular disease.

Data analysis. We conducted a series of linear regression models examining the cross-sectional associations between MCI and parkinsonism. Because scores on the measure of parkinsonism were positively skewed, the global and specific sign scores were subjected to a square root transformation for analyses. All models included terms to control for the potentially confounding effects of age, sex, and education; individuals taking antipsychotic medications (n = 4) were excluded from some subsequent models. Programming was done in SAS.[40]

Results. In the overall group, raw scores on the global measure of parkinsonism were positively skewed and ranged from 0 to 49, with higher scores indicating higher levels of parkinsonism. Because of their skewed distributions, the global and specific parkinsonian sign scores were subjected to a square root transformation for all analyses. The means and standard deviations (SD) of the transformed scores on the global measure of parkinsonism and the specific parkinsonian signs were as follows: global par-

Table 2 *Relation of MCI to parkinsonism**

Model term	Estimate	Standard error	*p* Value
Age	0.05	0.01	<0.001
Male	0.05	0.09	0.558
Education	−0.05	0.01	<0.001
MCI	0.26	0.09	0.004

* Estimated from a linear regression model.

MCI = mild cognitive impairment.

Table 3 *Relation of specific cognitive function measures to global parkinsonism among individuals with MCI**

	Effect on global parkinsonism			
Cognitive domain	Estimate	SE	*p* Value	R^2 change†
Episodic memory	−0.24	0.11	0.034	0.01
Semantic memory	−0.35	0.12	0.003	0.02
Working memory	−0.10	0.11	0.358	0.00
Perceptual speed	−0.42	0.08	0.001	0.08
Visuospatial ability	−0.16	0.09	0.080	0.00

* Estimated from separate linear regression models adjusted for age, sex, and education.
† Change in adjusted R^2 associated with the cognitive variable after accounting for the effects of age, sex, and education.

kinsonism: MCI = 3.1 (1.2), no cognitive impairment = 2.6 (1.2); gait: MCI = 4.4 (1.9), no cognitive impairment = 3.6 (1.9); rigidity: MCI = 1.3 (1.8), no cognitive impairment = 0.9 (1.7); bradykinesia: MCI = 3.2 (1.9), no cognitive impairment = 2.6 (2.0); and tremor: MCI = 1.0 (1.3), no cognitive impairment = 0.9 (1.4).

Presence of MCI and parkinsonism. We first conducted a series of linear regression models to examine whether the presence of MCI was associated with parkinsonism; individuals without cognitive impairment served as the reference group, and this and all subsequent models controlled for age, sex, and education. As shown in table 2, older age and fewer years of education were associated with higher levels of parkinsonism, and individuals with MCI exhibited higher levels of parkinsonism than individuals without cognitive impairment. The effect of MCI on parkinsonism was equivalent to the effect of about 5 additional years of age on parkinsonism.

In analyses examining the associations of MCI with each of the four parkinsonian signs, individuals with MCI exhibited more gait disturbance (estimate = 0.40, SE = 0.14, $p = 0.005$), bradykinesia (estimate = 0.38, SE = 0.16, $p = 0.014$), and rigidity (estimate = 0.28, SE = 0.13, $p = 0.035$) than individuals without cognitive impairment. Individuals with MCI did not differ from individuals without cognitive impairment in tremor (estimate = −0.09, SE = 0.11, $p = 0.395$).

Severity of cognitive impairment and parkinsonism. Next, we conducted a series of linear regression models restricted to those with MCI to examine whether the severity of cognitive impairment was associated with the overall degree of parkinsonism, using global cognitive function as an indicator of MCI severity. Lower cognitive function was associated with increased parkinsonism (estimate = −0.64, SE = 0.15, $p = 0.001$), with global cognition accounting for approximately 5% of the variance in the global measure of parkinsonism. This finding suggests that the severity of cognitive impairment is related to the overall degree of parkinsonism among individuals with MCI.

In analyses examining the associations between the severity of cognitive impairment and the four parkinsonian signs, lower cognitive function was associated with more impaired gait (estimate = −0.98, SE = 0.25, $p = 0.001$), bradykinesia (estimate = −0.62, SE = 0.27, $p = 0.021$), and tremor (estimate = −0.40, SE = 0.19, $p = 0.03$), with global cognitive function accounting for approximately 5% of the variance in gait, 1% in bradykinesia, and 2% in tremor. MCI severity was not strongly associated with rigidity (estimate = −0.37, SE = 0.28, $p = 0.185$).

Because the use of antipsychotic medications can contribute to parkinsonism and impair cognitive function, we repeated the core models reported above excluding individuals taking antipsychotics (n = 4). All associations of interest remained significant, suggesting that the results were not strongly influenced by the small number of participants taking antipsychotic medication.

Specific cognitive deficits and parkinsonism in MCI. Because cognition is not unitary and individuals with MCI have diverse cognitive deficits, we next conducted a series of linear regression analyses restricted to those with MCI to examine the associations between the level of function in the five cognitive domains (i.e., episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability) and the global measure of parkinsonism. As shown in table 3, lower levels of function in episodic memory, semantic memory, and perceptual speed were associated with higher levels of parkinsonism. Perceptual speed had the strongest effect, accounting for about 8% of the variance in the global measure of parkinsonism.

We repeated the above analyses for each of the specific parkinsonian signs. Lower levels of function in perceptual speed were associated with gait disturbance (estimate = −0.59, SE = 0.13, $p < 0.001$), bradykinesia (estimate = −0.47, SE = 0.14, $p = 0.001$), and tremor (estimate = −0.34, SE = 0.10, $p = 0.001$), with perceptual speed accounting for 3% to 5% of the variance in each sign. Semantic memory was associated with gait disturbance (estimate = −0.48, SE = 0.18, $p = 0.01$) and rigidity (estimate = −0.44, SE = 0.21, $p = 0.038$) but accounted for only 1 to 2% of the variance in those signs. Levels of impairment in other cognitive domains generally were not strongly related to the specific parkinsonian signs (additional information can be found on the *Neurology* Web site; go to www.neurology.org).

Although the above findings suggest that memory impairment is not strongly associated with parkinsonian signs in MCI, individuals with MCI commonly are classified on the basis of memory impairment and there is considerable research interest in the amnestic and non-amnestic subtypes of MCI. We therefore conducted linear regression analyses to examine whether the level of parkinsonian signs differed in amnestic vs non-amnestic MCI. Individuals with non-amnestic MCI differed from amnestic

MCI only on one parkinsonian sign, with non-amnestic MCI exhibiting more gait dysfunction than amnestic MCI (estimate = −0.76, SE = 0.33, $p = 0.024$).

Vascular factors and parkinsonian signs in MCI. Finally, because vascular risk factors and vascular disease can contribute to cognitive impairment and parkinsonian signs, we repeated the core models reported above adding terms to indicate each individual's overall vascular risk factor and vascular disease burden. As in the core models, individuals without cognitive impairment served as the reference group. The association between MCI and the global measure of parkinsonism remained significant and was essentially unchanged, even after controlling for the summary measures of vascular risk and vascular disease (adjusted estimate = 0.24, SE = 0.11, $p = 0.021$ vs the unadjusted estimate = 0.26, SE = 0.09, $p = 0.004$), and similar results were obtained for each of the four parkinsonian signs. Moreover, the associations between MCI and parkinsonian signs persisted even after accounting for the vascular risk and disease factors individually, suggesting that vascular factors do not explain the association between MCI and parkinsonism.

Discussion. In a community-based cohort of more than 800 individuals free of dementia and PD, we found that MCI was associated with parkinsonian signs and that the severity of cognitive impairment, particularly in the domain of perceptual speed, was strongly related to degree of parkinsonism among individuals with MCI. The associations between MCI and the parkinsonian signs remained significant and were essentially unchanged after accounting for vascular risk factors and vascular disease, suggesting that parkinsonism in MCI is not explained by vascular factors. Overall, these results suggest that MCI is accompanied by parkinsonian signs, the severity of which is related to the severity and type of cognitive impairment.

Several previous studies have shown that parkinsonian signs are common among individuals with[6-8] and without[1,2,4,5] dementia and are associated with cognitive decline,[3,4,8] dementia,[3,4] and death.[1,5,9] Only one prior study has examined parkinsonian signs among individuals with MCI[13]; results indicated that amnestic but not non-amnestic MCI is associated with mild parkinsonian signs, particularly rigidity. The present results extend those findings and suggest that MCI is associated with multiple parkinsonian signs, including gait disturbance, bradykinesia, and rigidity, with more severe parkinsonism among individuals with more severe cognitive impairment. Among the factors that could explain the discrepancy in study findings is the relatively modest effect size. Also, whereas the measure of parkinsonian signs used in the prior study[13] did not include gait or appendicular bradykinesia, we found that gait disturbance was most strongly associated with cognitive impairment. This finding is consistent with previous studies in which gait abnormalities have emerged as a robust predictor of cognitive impairment,[8,41] dementia,[41] and death.[1,5,41] Although the prognostic importance of gait disturbance in MCI is unknown, our findings suggest that gait disturbance may be an under-recognized yet important feature of MCI.

In contrast to the previous finding of a unique association between amnestic MCI and parkinsonism,[13] our results suggest that parkinsonian signs may be more prominent among individuals with non-amnestic forms of cognitive impairment as opposed to amnestic cognitive impairment. Compared to other cognitive domains, perceptual speed had the strongest and most consistent association with parkinsonian signs in MCI, particularly gait disturbance, indicating a relatively selective association between perceptual speed and parkinsonism in MCI. The reason for the discrepancy between findings is unclear, but it is noteworthy that previous cross-sectional findings[6] have also indicated selective associations between cognitive deficits consistent with frontostriatal dysfunction and parkinsonian signs. Our summary measure of perceptual speed includes tests sensitive to frontal systems (e.g., Stroop Test)[34,42] and nigrostriatal dysfunction (e.g., Digit Symbol Test),[30,43] and parkinsonism in MCI may in part reflect the disruption of frontal-subcortical circuits. It also is notable that the previous study used slightly different criteria for MCI; although the use of different criteria could influence study findings, the criteria used in these two studies were very similar overall, making it unlikely that this explains the discrepant findings.

The pathologic basis of parkinsonian signs in individuals without overt PD is not well understood. Parkinsonian signs in MCI may reflect the accumulation of AD pathology (e.g., neurofibrillary tangles) in the substantia nigra, as has been shown in AD.[44,45] Alternatively, parkinsonian signs in MCI may result from other pathologies, such as Lewy bodies, which have inconsistently been linked to motor impairment among individuals with and without dementia,[27,46-49] or from other lesions that affect dopaminergic pathways.[50] We also cannot exclude the possibility that subclinical cerebrovascular disease may be related to parkinsonism in MCI. Recent pathologic findings suggest that MCI may represent the earliest stages of dementia, especially AD,[11,12,51] and additional clinical-pathologic studies are required to determine the role of common age-related neuropathologies in the associations between cognitive function and parkinsonism in MCI.

This study has strengths and limitations. Strengths are the inclusion of a large, well-characterized cohort free of dementia and PD, the use of established and validated measures of cognitive function and parkinsonian signs, and the availability of data on multiple indicators of vascular risk factors and vascular disease burden. Limitations include the use of a selected sample, the use of self-report questions for some of the vascular factors, and cross-sectional analyses examining parkinsonism and cognitive function among individuals with MCI. Extension of these findings to longitudinal, community-based, clinical-pathologic studies will be

important to elucidate the neurobiologic basis and prognostic importance of parkinsonian signs in MCI.

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Orolingual angioedema associated with ACE inhibitor use after rtPA treatment of acute stroke

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Angioedema occurs in up to 5% of patients on angiotensin-converting enzyme inhibitor (ACEI) therapy receiving IV rtPA.[1] A 58-year-old man taking the combination ACEI amlodipine/benazepril received IV rtPA for clinical left middle cerebral artery territory acute infarction, NIHSS 9. Head CT was unremarkable. He developed orolingual angioedema 5 minutes after rtPA infusion was completed (figure). There was no airway compromise or hemodynamic instability to suggest anaphylactic reaction. Symptoms were treated with dexamethasone and a histamine antagonist. The angioedema resolved completely over the next 48 hours, as did his neurologic deficits.

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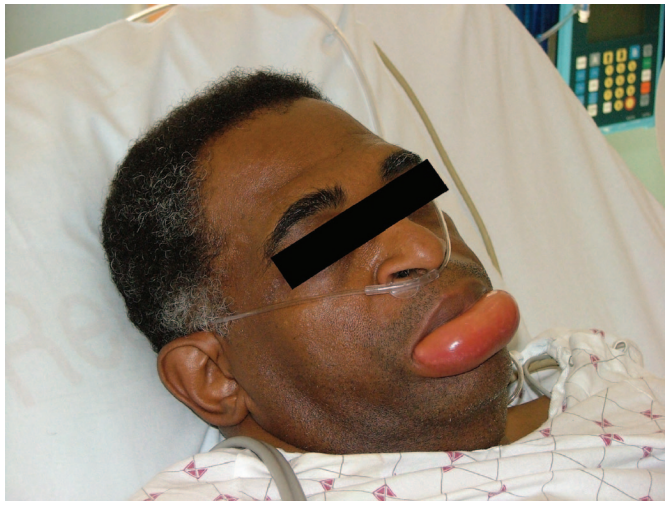

Figure. This patient developed severe orolingual angioedema involving predominantly the lower lip with apparent bilateral onset within 5 minutes of completing rtPA infusion. Erythrocyte sedimentation rate, immunoglobulin E, and complete cell count with differential were unremarkable.

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