Motor Dysfunction in Mild Cognitive Impairment and the Risk of Incident Alzheimer Disease

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Background: Little is known about motor function in mild cognitive impairment (MCI) and its relation to the risk of Alzheimer disease (AD).

Objective: To examine motor function in persons with MCI and its relation to risk of AD.

Design: Longitudinal cohort study.

Setting: More than 40 Catholic religious orders across the United States.

Participants: We studied 816 older Catholic clergy members from the Religious Orders Study. At the baseline evaluation, they were classified as having no cognitive impairment (n=558), MCI (n=198), or dementia (n=60).

Main Outcome Measures: Motor function was assessed at baseline using performance-based measures of upper and lower extremity function and a modified version of the motor section of the Unified Parkinson's Disease Rating Scale, from which previously established measures of parkinsonian signs were derived. Clinical evaluations for dementia and AD were repeated annually for up to 10 years. All analyses controlled for age, sex, educational level, and possession of at least 1 apolipoprotein E ε4 allele.

Results: At baseline, individuals with MCI had impaired motor function relative to those without cognitive impairment and superior motor function vs those with dementia. Among those with MCI, baseline levels of lower extremity motor performance, parkinsonian gait, and bradykinesia were inversely related to risk of AD, even after controlling for clinical stroke. Thus, a person with impaired lower limb performance or parkinsonian gait (10th percentile) was 2 to 3 times more likely to develop AD than a person with good lower limb function (90th percentile).

Conclusions: Persons with MCI also have impaired motor function, and the degree of impairment in lower extremity function is related to the risk of AD.

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A WIDE SPECTRUM OF COGNITIVE ability is seen in older persons, ranging from intact cognitive function to clinically manifested dementia. The term mild cognitive impairment (MCI) is increasingly used to refer to individuals who have some cognitive impairment but do not meet the criteria for dementia.1,2 Despite a lack of consensus about precisely how to define MCI, researchers agree that the condition is relatively common in older people.2,3 The presence of MCI is associated with an increased risk of Alzheimer disease (AD), but a substantial proportion of people with this heterogeneous condition do not develop dementia, underscoring the need to identify factors related to prognosis in MCI. Recent research4-6 suggests that motor function is impaired in people with MCI, but the relation of impaired motor function in MCI to subsequent risk of AD is not well understood.

In the present study, we used data from the Religious Orders Study7 to examine motor function in MCI. Participants were older Catholic nuns, priests, and brothers. At baseline, they underwent a uniform evaluation that included clinical classification of MCI and AD, performance-based tests of upper and lower extremity motor function, and a semiquantitative assessment of parkinsonian motor signs. In our analyses, we examined the relation of MCI to baseline motor function, the relation of baseline motor function in MCI to risk of incident AD, and whether clinically diagnosed stroke accounted for the presence or consequences of motor dysfunction in MCI.

METHODS

Participants

All the participants are from the Religious Orders Study, an investigation of aging and AD among older Catholic nuns, priests, and broth-
ers. Participants without known dementia signed an informed consent form agreeing to annual clinical evaluations and an anatomical gift act for brain donation at death. The study was approved by the institutional review board of Rush University Medical Center.

Clinical evaluations began in January 1994 and are continuing. At the time of these analyses, 816 persons had completed the baseline clinical evaluation. Of these, 60 met the criteria for AD, 598 had no cognitive impairment, and 198 met the criteria for MCI, as described later herein. These 816 persons had a mean (SD) age of 76.1 (7.1) years, a mean (SD) of 18.1 (3.4) years of education, and a mean (SD) Mini-Mental State Examination score of 28.0 (2.4) at baseline; 66.2% were women and 92.4% were white and non-Hispanic.

Of the 198 people with MCI, 9 had not yet reached their first follow-up date at the time of these analyses. All the remaining 189 persons participated in at least 1 follow-up evaluation, with a mean of 7.2 evaluations per individual (because the study has ongoing enrollment, the number of evaluations ranged from 2 to 11).

CLINICAL EVALUATION

At baseline, each participant underwent a uniform clinical evaluation that included a medical history, neurologic examination, cognitive function assessment (see the following subsection), and review of the brain scan if available (through 2002). Clinical classification of MCI, dementia, and AD was based on these data, as previously described.1,8,9 A board-certified clinical neuropsychologist, blinded to the person's age, sex, and race, reviewed the results of all cognitive tests and data on educational level, occupation, sensory and motor deficits, and effort and rendered a clinical judgment regarding the presence of impairment in episodic memory and other cognitive domains. An experienced health care professional evaluated each participant and made diagnostic decisions based on a review of all available data. The diagnoses of dementia and AD followed the criteria of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association.10 These criteria require a history of cognitive decline and impairment in at least 2 cognitive domains, 1 of which must be memory, for a diagnosis of AD.

There are no consensus criteria for the clinical classification of MCI. The classification system used in this study has been previously described.1,8,9,11,12 The diagnosis of MCI was based on 2 criteria: (1) the presence of cognitive impairment as determined by a neuropsychologist after a review of raw test scores and educationally adjusted impairment ratings2 and (2) the absence of dementia as determined by an experienced health care professional based on a review of all available clinical data and an in-person evaluation of the participant. These criteria are similar to those used in the Canadian Study of Health and Aging to define cognitive impairment without dementia13 and differ from the criteria of Petersen et al14 in that they do not require a memory complaint or intact activities of daily living or that cognitive impairment be in episodic memory. The clinical diagnosis of stroke was based on the medical history and neurologic examination findings supplemented by neuroimaging when available, as previously described.14

ASSESSMENT OF COGNITIVE FUNCTION

Twenty cognitive performance tests were administered as part of each evaluation. The Mini-Mental State Examination,15 a measure of global cognition, was used for descriptive purposes but not in analyses. Seven tests assessed episodic memory: immediate and delayed recall of the East Boston Story,16,17 and Story A from Logical Memory,18 and Word List Memory, Recall, and Recognition.19 Semantic memory was assessed using a 20-item version of the Boston Naming Test,20 a 15-item form of Extended Range Vocabulary,21 and a 20-item form of the National Adult Reading Test.22 There were 4 tests of working memory: Digit Ordering,23 Alpha Span,24 and Digit Span Forward and Backward.25 Perceptual speed was assessed using the oral version of the Symbol Digit Modalities Test26 and Number Comparison,27 and visuospatial ability was evaluated using a 15-item version of Judgment of Line Orientation28 and a 17-item version of Standard Progressive Matrices.29

Composites of 2 or more tests were used in the analyses to reduce measurement error in general and floor and ceiling artifacts in particular. We formed measures of episodic memory (based on 7 tests), semantic memory (4 tests), working memory (4 tests), perceptual speed (2 tests), and visuospatial ability (2 tests). Raw scores on each component test were converted to z scores using the baseline mean (SD) from all participants in the Religious Orders Study and were averaged to form the composite measures. Further information on the individual tests and on the derivation and psychometric properties of these composite measures is contained in previous publications.16,27,30

ASSESSMENT OF MOTOR FUNCTION

We assessed lower limb function using 5 performance-based measures, as previously described.30 Each measure was scaled from 0 to 5, with higher scores indicating better performance and 0 indicating an inability to perform the task. We asked participants to walk 8 feet (2.43 m) at a normal pace and measured the time and number of steps taken. Each distribution was divided into quintiles, with scores of 5 assigned to the fastest walking speeds and fewest walking steps and scores of 1 to the slowest speeds and most steps. Participants were asked to stand up and sit down 5 times in a chair. Those who attempted but could not complete the tasks were given a score of 1. The time taken to successfully complete the task was divided into quartiles, and scores of 2 to 5 were assigned, with higher scores for faster quartiles. To assess standing balance, we asked the participants to stand in each of 4 positions for up to 10 seconds: full-tandem stand (ie, heel to toe) with eyes open, semitandem stand (ie, heel of 1 foot astride the toes of the other) with eyes open, and side-by-side stand (ie, feet aligned and touching) with eyes open and with eyes closed. Total time on the 4 tasks was divided into quintiles, with 5 assigned to those maintaining balance the longest. Because the resulting 5 measures were moderately correlated (median r=0.45), we averaged them to create a global measure of lower limb function.

Upper extremity motor function was assessed using the Purdue Pegboard Test,31 a widely used measure of manual dexterity.32 The participant placed as many pegs in holes on the board as possible during each of 4 30-second trials, 2 with the right hand and 2 with the left hand. The score was the mean number of pegs correctly placed during each trial.

We also assessed motor function using a modified version33,34 of the motor portion of the Unified Parkinson's Disease Rating Scale.35 Nurse clinicians administered the scale to participants after completing a structured training program, as previously described.35 Four parkinsonian signs were derived: gait disorder (based on 6 items), rigidity (based on 5 items), bradykinesia (based on 4 items), and tremor (based on 2 items); sign scores ranged from 0 to 100 and represent the percentage of the total possible score obtained. A global measure of parkinsonism was calculated by averaging the 4 sign scores. In previous research, these measures were shown to have high in-
tarrant reliability and short-term temporal stability.\textsuperscript{33} All parkinsonian sign scores were analyzed using a square root transformation because of their skewed distributions.

**APOLIPOPROTEIN E GENOTYPING**

Apolipoprotein E genotyping was performed blinded to all other study data using methods adapted from Hixson and Vernier\textsuperscript{16} and primers described by Wenham et al,\textsuperscript{37} as reported elsewhere.\textsuperscript{2} In all the analyses, persons were dichotomized into those with at least 1 copy of the ε4 allele (ie, ε2/4, ε3/4, or ε4/4) vs those without an ε4 allele (ie, ε2/2, ε2/3, or ε3/3).

**DATA ANALYSIS**

Separate linear regression models were constructed to compare the levels of performance-based and parkinsonian motor measures among the 3 diagnostic groups. In these analyses, participants with MCI served as the reference group, which was contrasted with those without cognitive impairment and those with dementia. These and all subsequent analyses controlled for age, sex, educational level, and possession of at least 1 copy of the apolipoprotein E ε4 allele. In subsequent linear regression analyses, persons with AD were excluded and those without cognitive impairment were contrasted with 2 subgroups: MCI with stroke and MCI without stroke.

Proportional hazards models\textsuperscript{38} were used to separately assess the relation of each performance-based and parkinsonian motor measure at baseline to risk of AD during follow-up among persons with MCI at baseline. Each analysis was then repeated with a term added for the presence of clinically diagnosed stroke. Model assumptions were graphically and analytically examined and were found to be adequately met. Programming was performed using SAS software.\textsuperscript{39}

**RESULTS**

**METRIC PROPERTIES OF MOTOR FUNCTION MEASURES**

Purdue Pegboard scores ranged from 0 to 19.3 (mean [SD], 9.7 [2.5]) and lower extremity function ranged from 0.2 to 5.0 (mean [SD], 2.7 [1.2]), with higher scores indicating better performance. Pegboard score was moderately correlated with lower limb score (r=0.57; P<.001). Age was inversely related to pegboard performance (r = −0.48) and lower limb function (r = −0.55) (P<.001 for both); educational level was positively related to pegboard score (r=0.10; P=.004) and lower limb function (r=0.11; P=.001). Women had better pegboard performance than men (t\textsubscript{df}=4.73), whereas men had better lower extremity function than women (t\textsubscript{df}=5.11) (P<.001 for both).

Because of their skewed distributions, the global and specific parkinsonian sign scores were subjected to a square root transformation for all analyses. The mean (SD) transformed scores were as follows: global parkinsonism, 2.53 (1.28); gait, 3.05 (2.02); rigidity, 0.84 (1.61); bradykinesia, 2.99 (1.92); and tremor, 1.08 (1.45). The global parkinsonian sign score was inversely related to lower limb function (r = −0.61; P<.001) and pegboard performance (r = −0.58; P<.001). Age (r = 0.48; P<.001), but not educational level (r = −0.05; P=.15), was positively related to global parkinsonian, and no sex differences were noted.

**MOTOR FUNCTION IN MCI**

Of 816 participants at baseline, 558 had no cognitive impairment, 198 had MCI, and 60 met the clinical criteria for AD (Table 1). Persons with MCI were younger than those with AD and older than those without cognitive impairment. The diagnostic subgroups did not differ in educational level or sex.

Upper and lower limb motor functions in participants with MCI were intermediate in relation to those of participants without cognitive impairment and those with AD (Figure 1). To determine whether level of motor function differed among the 3 diagnostic groups, we constructed separate linear regression models for each motor measure. In each model, MCI served as the reference group, which was contrasted with the subgroup without cognitive impairment and the subgroup with AD, controlling for age, sex, educational level, and possession of at least 1 ε4 allele (Table 2). On both performance-based motor measures, the MCI group was impaired relative to those without cognitive impairment and superior to those with AD.

Because stroke is associated with motor dysfunction and was more common in the MCI subgroup than in those without cognitive impairment, we constructed separate linear regression models for the upper and lower extremity motor measures, in which individuals without cognitive impairment were contrasted to those with MCI with stroke (n=23) and those with MCI without stroke (n=166). In participants with MCI with stroke, lower (estimate [SE]=−0.80 [0.21]; P<.001) and upper (estimate [SE]=−1.20 [0.44]; P=.006) extremity motor functions were impaired. In participants with MCI without stroke, by contrast, neither lower (estimate [SE]=−0.10 [0.09]; P=.24) nor upper (estimate [SE]=−0.33 [0.19]; P=.18) limb function was reduced relative to participants without cognitive impairment.

The level of global parkinsonism in participants with MCI was intermediate in relation to that of those without cognitive impairment and those with AD (Figure 2). To analyze these effects, we constructed identical linear regression models comparing participants with MCI with the subgroup without cognitive impairment and the subgroup with AD, controlling for age, sex, and educational level (Table 2). Individuals with MCI exhibited less global parkinsonism than individuals with AD and more global parkinsonism than those without cognitive impairment. Similar effects were seen for gait disturbance and bradykinesia; rigidity in MCI was reduced compared with the AD subgroup but did not differ from the

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**Table 1. Characteristics of Religious Orders Study Participants at Baseline**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Cognitive Impairment (n = 558)</th>
<th>Mild Cognitive Impairment (n = 198)</th>
<th>Alzheimer Disease (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>74.6 (6.7)</td>
<td>78.7 (7.0)</td>
<td>81.9 (6.7)</td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>18.3 (3.4)</td>
<td>17.8 (3.3)</td>
<td>16.9 (3.10)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>33.7</td>
<td>32.8</td>
<td>38.3</td>
</tr>
</tbody>
</table>

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subgroup without cognitive impairment; there was no effect for tremor (Table 2).

Compared with participants without cognitive impairment, global parkinsonism was impaired in the MCI subgroup with stroke (estimate [SE] = 0.62 [0.22]; P = .005) but not in the subgroup without stroke (estimate [SE] = 0.14 [0.09]; P = .14). The MCI subgroup with stroke also showed impairment in parkinsonian gait (estimate [SE] = 1.37 [0.36]; P < .001) but not in other parkinsonian signs, and no increase in parkinsonian signs was seen in the MCI subgroup without stroke.

**Table 2. Relationship of Mild Cognitive Impairment to Performance-Based and UPDRS-Based Motor Function at Baseline**

<table>
<thead>
<tr>
<th>Motor Measure</th>
<th>Model Term</th>
<th>Estimate (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance based</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper limb</td>
<td>MCI vs no CI</td>
<td>0.47 (0.18)</td>
<td>.01</td>
</tr>
<tr>
<td>MCI vs AD</td>
<td>–1.15 (0.32)</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>Lower limb</td>
<td>MCI vs no CI</td>
<td>0.19 (0.09)</td>
<td>.03</td>
</tr>
<tr>
<td>MCI vs AD</td>
<td>–0.56 (0.15)</td>
<td>&lt; .001</td>
<td></td>
</tr>
<tr>
<td>UPDRS based</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait</td>
<td>MCI vs no CI</td>
<td>–0.27 (0.15)</td>
<td>.07</td>
</tr>
<tr>
<td>MCI vs AD</td>
<td>0.64 (0.26)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>MCI vs no CI</td>
<td>–0.34 (0.15)</td>
<td>.02</td>
</tr>
<tr>
<td>MCI vs AD</td>
<td>0.78 (0.26)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Rigidity</td>
<td>MCI vs no CI</td>
<td>–0.02 (0.13)</td>
<td>.90</td>
</tr>
<tr>
<td>MCI vs AD</td>
<td>0.57 (0.23)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>MCI vs no CI</td>
<td>–0.06 (0.12)</td>
<td>.64</td>
</tr>
<tr>
<td>MCI vs AD</td>
<td>0.14 (0.21)</td>
<td>.50</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CI, cognitive impairment; MCI, mild cognitive impairment; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Estimated from separate linear regression models adjusted for age, sex, educational level, and possession of at least 1 apolipoprotein E ε4 allele.

**Table 3. Relationship of Motor Function in Mild Cognitive Impairment to Risk of Incident Alzheimer Disease**

<table>
<thead>
<tr>
<th>Motor Variable</th>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gait</td>
<td>0.79 (0.64-0.97)</td>
<td>0.76 (0.62-0.95)</td>
</tr>
<tr>
<td>Purdue pegboards</td>
<td>0.99 (0.90-1.09)</td>
<td>0.99 (0.90-1.09)</td>
</tr>
<tr>
<td>UPDRS based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global parkinsonism</td>
<td>1.04 (1.01-1.07)</td>
<td>1.04 (1.01-1.07)</td>
</tr>
<tr>
<td>Gait</td>
<td>1.02 (1.00-1.03)</td>
<td>1.02 (1.00-1.04)</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>1.02 (1.00-1.04)</td>
<td>1.02 (1.00-1.04)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>1.01 (0.99-1.04)</td>
<td>1.01 (0.99-1.04)</td>
</tr>
<tr>
<td>Tremor</td>
<td>1.01 (0.97-1.05)</td>
<td>1.00 (0.97-1.05)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk; UPDRS, Unified Parkinson’s Disease Rating Scale.

*Estimated from separate Cox proportional hazards models adjusted for age, sex, educational level, and apolipoprotein E ε4 allele (model A) and also stroke (model B).

**RELATIONSHIP OF MOTOR FUNCTION IN MCI TO RISK OF AD**

Given evidence that motor function is impaired in MCI, we next examined whether level of motor impairment was associated with subsequent risk of AD in analyses restricted to participants with MCI. Accordingly, we constructed proportional hazards models adjusted for age, sex, educational level, and possession of an ε4 allele (Table 3, model A). Upper extremity motor function was not related to risk of AD, but lower extremity motor...
We found that motor function in those with MCI was impaired relative to that of persons with no cognitive impairment and superior to persons with AD. Among those with MCI, level of gait dysfunction and motor slowing predicted risk of AD during a mean of more than 6 years of observation. The results suggest that MCI is characterized by motor dysfunction and cognitive impairment and that the degree of motor impairment, particularly gait dysfunction, may help identify those at risk for AD.

Previous research on motor function in MCI has been limited. Cross-sectional studies have reported defective equilibrium, limb coordination, handwriting, and parkinsonian signs in persons with MCI relative to those without cognitive impairment, consistent with the results of this study. We are unaware of previous research linking motor dysfunction in MCI to risk of incident AD, but past studies have shown an association between decline in motor and cognitive function in older persons with and without dementia, consistent with the present results.

The factors contributing to motor dysfunction in MCI are uncertain. At baseline in this study, clinically diagnosed stroke seemed to account for the impaired manual dexterity and lower limb dysfunction in those with MCI relative to persons without cognitive impairment. These findings are in agreement with previous cross-sectional research showing that motor dysfunction in older people in general and in those with MCI in particular is associated with cerebrovascular disease. Specifically, periventricular white matter lesions in the frontal lobe have been associated with gait and balance problems in MCI. On the other hand, the risk of AD during follow-up was associated with severity of lower limb dysfunction even after controlling for clinical stroke, suggesting that factors in addition to stroke may be contributing to the development of AD in individuals with MCI. One possibility is that AD abnormalities are contributing to disordered gait and bradykinesia. For example, neurofibrillary tangles in the substantia nigra have been related to gait disturbance in older persons with and without dementia in AD. In addition, AD abnormalities are known to accumulate in other motor regions, including the primary motor cortex and striatum. Additional clinicopathologic and clinicoradiologic studies of the neurobiologic basis of motor dysfunction in MCI are needed to investigate these relationships.

Confidence in these findings is strengthened by several factors. Clinical classification of MCI and AD was based on a uniform clinical evaluation and on the application of widely used criteria by experienced health care professionals, reducing the likelihood that diagnostic bias or imprecision affected the results. Upper and lower extremity motor abilities were assessed using established composite measures. The availability of nearly 200 people with MCI with a mean of more than 6 years of follow-up and high follow-up participation enhanced our power to detect associations between motor performance and disease incidence.

The main limitation of these findings is that they are based on a selected group of participants who differ in...
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Author Contributions: Study concept and design: Wilson and Bennett. Acquisition of data: Aggarwal, Wilson, and Bennett. Analysis and interpretation of data: Aggarwal, Wilson, Beck, Bienias, and Bennett. Drafting of the manuscript: Aggarwal and Wilson. Critical revision of the manuscript for important intellectual content: Aggarwal, Wilson, Beck, Bienias, and Bennett. Statistical analysis: Aggarwal, Beck, and Bienias. Obtained funding: Wilson and Bennett. Administrative, technical, and material support: Wilson and Bennett. Study supervision: Aggarwal and Bennett.

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mor-

Announcement

Calendar of Events: A New Web Feature

On the new Calendar of Events site, available at http://pubs.ama-assn.org/cgi/calendarcontent and linked off the home page of the Archives of Neurology, individuals can now submit meetings to be listed. Just go to http://pubs.ama-assn.org/cgi/cal-submit/ (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.