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Mild Parkinsonian Signs Are Associated with Increased Risk of Dementia in a Prospective, Population-Based Study of Elders

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Abstract

Introduction—There is some evidence that mild Parkinsonian signs (MPS) are associated with increased risk of dementia, suggesting that MPS could be an early biomarker for dementia.

Objective—In a new cohort, to determine whether (1) baseline MPS are a predictor of incident dementia, (2) there is an interaction between MPS and other baseline risk factors for dementia (i.e., the presence of both together greatly elevates the risk of dementia).

Methods—In a prospective, longitudinal study of community-dwelling elders in northern Manhattan, NY, Parkinsonian signs were rated with an abbreviated Unified Parkinson's Disease Rating Scale. Risk of incident dementia was assessed using Cox proportional hazards models.

Results—There were 1,851 participants (mean follow-up = 3.7 years). Participants with baseline MPS were twice as likely to develop dementia as participants without MPS: 16.3% vs. 7.7%, unadjusted hazards ratio (HR) = 2.24 ($p < 0.001$), adjusted HR = 1.98 ($p < 0.001$). MPS were divided into three subtypes: adjusted HR_{axial dysfunction} = 2.45 ($p < 0.001$), adjusted HR_{tremor} = 2.38 ($p = 0.006$), and adjusted HR_{rigidity} = 1.16 ($p = 0.58$). When MPS were treated as a continuous variable, the adjusted HR = 1.15 ($p = 0.001$). There were no interactions between MPS and other

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Statistical Analyses: The statistical analyses were conducted by Dr. Louis.

Author Contributions

Elan D. Louis: Research project conception, organization and execution; statistical analyses design and execution; manuscript writing (writing the first draft and making subsequent revisions).

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baseline risk factors for dementia, including gender, education, race, family history of dementia, stroke, and APOE-e4.

Conclusions—Baseline MPS seem to be a predictor of incident dementia. These motor signs might therefore serve as a useful biomarker for emerging dementia.

Keywords

mild parkinsonian signs; population; elderly; epidemiology; incident dementia; Alzheimer's disease

INTRODUCTION

Mild Parkinsonian signs (MPS) are commonly found during the clinical examination of older people without known neurological disease, with the most common of these being impaired gait and balance, followed by rigidity and bradykinesia, and least commonly rest tremor.¹⁻⁴ These signs are associated with functional disability^{5, 6} and increased risk of mortality.^{1, 7} In recent years, both the Religious Orders Study³ and the Washington Heights-Inwood Columbia Aging Project (WHICAP)⁸ have demonstrated an association between the presence of MPS in non-demented elders and the development of incident dementia during prospective follow-up. These two initial studies, one of which was population-based,⁸ suggest that MPS might be a biomarker for future dementia. A second set of prospective, population-based data are now available. The current WHICAP cohort represents a combination of continuing members of the cohort originally recruited between 1992 and 1996,⁸ and members of a new cohort recruited between 1999 and 2001; approximately three-quarters of the sample was from the new cohort.

Using data from the new WHICAP cohort recruited between 1999 and 2001, we addressed two questions. First, is there an association between MPS assessed at the initial visit in non-demented participants and risk of incident dementia? If so, this would represent a second population-based study in which this association has been demonstrated. Second, if MPS are a risk factor for dementia, then what is the relationship between MPS and other more well-established risk factors for dementia (e.g., education, family history of dementia, APOE-e4 status)? More specifically, is there an interaction between MPS and other risk factors for dementia such that the presence of both together greatly elevates the risk of developing dementia? Identification of such interactions is important as it allows physicians to identify individuals with specific constellations of risk factors that place them at very high risk of developing dementia.

METHODS

Study population

2,776 individuals participated in a prospective study of aging and dementia in Medicare-eligible northern Manhattan residents, age 65 years and older (WHICAP). The current WHICAP cohort represents a combination of continuing members of the cohort originally recruited between 1992 and 1996 ($n = 602$) and members of a new cohort recruited between 1999 and 2001 ($n = 2,174$).^{9, 10} Participants in WHICAP were drawn by random sampling of healthy Medicare beneficiaries aged ≥ 65 years residing within a geographically-defined area of northern Manhattan (New York City); the sampling strategies and recruitment outcomes have been described in detail elsewhere.¹¹ As data on the original 1992 cohort have been reported in the past,⁸ the current analyses were restricted to the new cohort recruited between 1999 and 2001 ($n = 2,174$) whose mean age was 76.9 years, mean education was 10.3 years, 66.7% were women and 36.4% were Hispanic. Each participant

underwent a structured medical interview and a standardized neurological examination, which included an abbreviated (ten-item) version of the motor portion Unified Parkinson's Disease Rating Scale (UPDRS)¹² and a standardized neuropsychological battery.⁹ Participants have been followed at approximately 18-month intervals with similar assessments at each interval. Recruitment, informed consent and study procedures were approved by the Columbia University Institutional Review Board.

For these analyses we excluded 120 individuals who did not have complete neurological examination data. We then excluded 2 participants with incomplete neuropsychological data and 183 additional individuals who were demented at baseline. We also excluded anyone with Parkinson's disease (PD) or Parkinson Plus syndrome. We assigned a diagnosis of PD or Parkinson Plus syndrome based on research criteria¹³ and participants were considered to have PD or Parkinson Plus syndrome if (1) they had previously received one of these diagnoses, or (2) they had two or more cardinal signs of parkinsonism on the standardized neurological examination. Cardinal signs were bradykinesia, rigidity, rest tremor, and postural changes. A cardinal sign was considered to be present when one UPDRS rating was ≥ 2 . Eighteen (0.96%) of the remaining 1,869 participants had a diagnosis of PD or a Parkinson Plus syndrome, consistent with the reported prevalence (approximately 1%) of these disorders in other elderly population-based samples¹⁴ and in previous studies in northern Manhattan.¹⁵

After these three exclusions, the final sample was 1,851 participants. These 1,851 had a mean age of 76.1 years, mean education = 10.7 years, and 66.3% were women and 34.5% were Hispanic.

Evaluation

A trained research assistant collected demographic information and administered a structured interview of health (e.g., hypertension, diabetes mellitus, stroke, etc, all by self-report). Each participant also underwent a standardized neurological examination, which included an abbreviated (ten-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS).^{12, 16} The abbreviated UPDRS included evaluations of speech, facial expression, tremor at rest (in any body region), rigidity (rated separately in the neck, right arm, left arm, right leg, and left leg), changes in posture, and body (axial) bradykinesia.¹⁶ Each of the ten items was rated from 0 – 4. A Parkinsonian sign score (range = 0 [no Parkinsonian signs] – 40 [maximum]) was calculated for each participant. The general medical doctors who administered the modified motor portion of the UPDRS were trained using a structured protocol.⁸ Inter-rater reliability of their ratings was adequate (weighted kappa statistics for ratings of speech, facial expression, tremor at rest, posture, and axial bradykinesia = 0.65 – 0.90) and agreement (percent concordance) with a senior movement disorder neurologist's ratings (E.D.L.) was 79%.¹⁶

As in previous analyses,^{16–18} MPS were defined as present when any one of the following conditions was met: (1) two or more UPDRS ratings = 1 or (2) one UPDRS rating ≥ 2 or (3) the UPDRS rest tremor rating = 1. Based on a factor analysis,¹⁹ MPS was stratified into three subtypes: axial dysfunction (changes in speech, facial expression, changes in posture, and axial bradykinesia), rigidity, and tremor. An abnormality in axial function was considered present when the participants had either: (1) UPDRS ratings = 1 in two or more axial function items or (2) one UPDRS axial function rating ≥ 2 . Rigidity was considered present when the participants had either: (1) UPDRS ratings = 1 in two or more rigidity items or (2) one UPDRS rigidity rating ≥ 2 . Tremor was considered present when the participants had a UPDRS rest tremor rating = 1.¹⁶

As previously described,²⁰ all participants also underwent a standardized neuropsychological battery.⁹ Dementia diagnoses, assigned by consensus conference of neurologists and neuropsychologists, were based on a neuropsychological battery and the physician-administered neurological examination.²¹ Participants were considered demented if, based on neuropsychological testing, they demonstrated impairment in memory and at least two other cognitive domains, in the absence of delirium.^{21, 22} As in other studies of this cohort,^{23, 24} criteria for dementia from the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) were applied in addition to ancillary information from medical charts and lab studies in the final evaluation.²⁵ Evidence of deficits in social or occupational functioning, as assessed by the Blessed Dementia Rating Scale²⁶ and the Schwab and England Activities of Daily Living Scale,²⁷ was also required for the consensus diagnosis. The type of dementia was subsequently determined. Diagnosis of probable or possible Alzheimer's disease (AD) was based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria.²⁸

Based on the neuropsychological test battery, participants were assigned diagnoses of mild cognitive impairment (MCI) according to published criteria.^{29–32} The Center for Epidemiologic Study Depression (CESD) scale assessed depressive symptoms; as done previously, scores ≥ 4 were coded as depressed.^{33, 34}

Statistical analyses

All statistical analyses were performed in SPSS (Version 16.0), including chi-square and t tests. Cox proportional hazards regression, which yielded hazard ratios (HRs), compared the risk of developing incident dementia in participants with vs. without MPS at their initial visit. The time-to-event variable was time from baseline examination to diagnosis of dementia, and all models adjusted for age. In fully adjusted models, we also included variables that were associated with either MPS or dementia at $p < 0.05$ (Tables 1 and 2) or for which prior evidence suggested that this variable could be a confounder. We also performed several additional Cox analyses. First, the Parkinsonian sign score (a continuous variable) was used and, in these Cox models, we evaluated the risk of developing incident dementia based on baseline Parkinsonian sign score. Second, we performed a Cox analysis in which we removed participants with MCI at baseline. Third, we examined the risk of incident AD; in this Cox model, incident AD was coded as 1 while non-dementia and other causes of dementia were coded as 0. Fourth, in several Cox models, data from the modified UPDRS were stratified into three subtypes (axial dysfunction, rigidity, and tremor) (Table 3). Fifth, we examined the association between MPS to incident MCI in Cox proportional hazards models; these models removed participants with baseline MCI. Finally, using Cox models, we also looked for interactions between MPS and other baseline factors that, in the published literature, ^{35–38} have been reported to be associated with increased risk of dementia (gender, education, ethnicity, family history of dementia, stroke, diabetes mellitus, heart disease, and APOE-e4 status). In each of these Cox models (Table 4), we included MPS, age, the main term (e.g., education) and the interaction term (e.g., MPS*education).

We also used longitudinal data to examine the relation of MPS to change in four cognitive function domains (language, memory, processing speed, and visuo-spatial). The development of factor scores for these domains has been described.³⁹ These analyses were performed by applying generalized estimating equations to regression analyses with repeated measures.⁴⁰ Generalized estimating equations allowed us to quantify the average annual rate of decline of each cognitive measure and determine whether MPS, as a baseline factor, was a significant predictor of these cognitive measures. We examined baseline MPS (main effect) and its interaction with time. We hypothesized a more rapid cognitive decline in those with MPS.

RESULTS

The 1,851 participants had a mean duration of follow-up of 3.7 years (maximum = 9.0 years). The mean baseline Parkinsonian sign score was 0.65 (range = 0 – 14) and MPS were present in 270 (14.6%).

At baseline, participants with MPS were older and had fewer years of education than those without MPS; also, a larger proportion of participants with MPS had diabetes mellitus, heart disease and stroke (Table 1). Participants with MPS did not differ from those without MPS in terms of race, smoking and several other variables (Table 1),

Of the 1,851 participants, 165 (8.9%) developed dementia. At baseline, they were older, had fewer years of education, and more likely to have had a stroke, have diabetes mellitus, and be depressed, and less likely to be non-Hispanic White; however, they did not differ with regards to gender, smoking and several other factors (Table 2). Of these 165, 152 (92.1%) had clinical diagnoses of AD.

The proportion of participants with baseline MPS who developed incident dementia was more than double that of participants without baseline MPS (44 [16.3%] vs. 121 [7.7%], chi-square = 21.22, $p < 0.001$). Of the 44 participants with MPS and dementia, 38 (86.4%) had AD, and of the 121 participants without MPS who were demented, 114 (94.2%) had AD.

In a Cox proportional hazards model that adjusted for age, the hazards ratio (HR) for dementia was approximately two-fold for those with MPS compared with those without MPS: 2.24 (95% confidence interval [CI] = 1.57 – 3.20, $p < 0.001$). In a Cox model that adjusted for age, race, education, depression, diabetes mellitus, heart disease, stroke, and arthritis, the HR was 1.98 (95% CI = 1.37 – 2.88, $p < 0.001$). We also performed several additional Cox analyses. First, we performed analyses in which the Parkinsonian sign score, a continuous variable, was used rather than MPS, which was a dichotomous variable. In a Cox proportional hazards model that adjusted for age, the Parkinsonian sign score was associated with increased risk of dementia: HR = 1.18 (95% CI = 1.09 – 1.26, $p < 0.001$). In a fully adjusted model (age, race, education, depression, diabetes mellitus, heart disease, stroke, and arthritis), the results were similar: HR = 1.15 (95% CI = 1.06 – 1.25, $p = 0.001$), meaning that with each one point increase in the Parkinsonian sign score, the risk of incident dementia increased by 15%. Second, as MCI may be a precursor to dementia, we removed all 408 participants with MCI at baseline; 1,443 participants remained and, in these, in the fully adjusted model (adjusted for age, race, education, depression, diabetes mellitus, heart disease, stroke, and arthritis) the HR was 1.89 (95% CI = 1.20 – 3.00, $p = 0.007$). Third, we examined the risk of AD in the 1,851 participants; in a fully adjusted model, the HR was 1.78 (95% CI = 1.20 – 2.65, $p = 0.004$). Fourth, MPS were stratified into subtypes (Table 3) and, in fully adjusted Cox models, baseline axial dysfunction and baseline tremor were associated with increased risk of dementia. Fifth, we examined the association between MPS and incident MCI. In a Cox proportional hazards model that adjusted for age, there was no association between MPS and incident MCI: HR = 0.80 (95% CI = 0.55 – 1.18, $p = 0.27$). In a fully adjusted model, the results were similar: HR = 0.80 (95% CI = 0.54 – 1.20, $p = 0.28$).

We also used longitudinal data to examine the relation of baseline MPS to change in four cognitive measures (language, memory, processing speed, and visuo-spatial). These analyses showed that the presence of MPS at baseline was a significant predictor of more rapid annual rate of decline of language ($p = 0.001$) and memory ($p = 0.025$); MPS was marginally associated with more rapid annual rate of decline of processing speed ($p = 0.067$) but not visuo-spatial function ($p = 0.80$).

We also looked for interactions between MPS and other baseline risk factors for dementia (Table 4). None of the interaction terms was associated with increased risk of dementia.

DISCUSSION

In this prospective study of elders, MPS were a robust predictor of incident dementia. In both unadjusted and adjusted analyses, participants with MPS were twice as likely to develop incident dementia as their peers without these neurological signs. Indeed, with each one point increase in the Parkinsonian sign score, the risk of incident dementia increased by 15%. These data are in agreement with two earlier cohort studies reporting similar findings, 3⁸ one of which was population-based.⁸ Along with reports that MPS are associated with an increased risk of mortality,^{1⁷} the current data indicate that MPS, though mild, are not prognostically benign.

The pathological basis for MPS and for the reported association between MPS and incident dementia is not entirely clear. Several lines of data suggest that MPS, in some cases, could be a marker for tangle pathology in the basal ganglia. For example, the majority of individuals with MPS who progress to dementia develop AD rather than other forms of dementia.^{2⁵7} Thus, in the Religious Orders Study,³ 95.6% of participants who developed incident dementia carried clinical diagnoses of AD. Also, it is well known that patients who have prevalent AD commonly manifest MPS⁴¹ and that these signs are often progressive. In a post-mortem study at Columbia University⁴¹ the numbers of nigral neurofibrillary tangles and neuropil threads were increased in the 18 AD patients with MPS (including rigidity and resting tremor) compared to the 10 AD patients without MPS. Data from Washington University found a number of pathologies in the substantia nigra that related to severity of MPS (including rigidity, rest tremor, bradykinesia, parkinsoniangait) in AD patients; these included neuronal loss and neurofibrillary tangles.⁴²

As in previous studies,^{3⁸} the association between MPS and risk of dementia was particularly robust among participants with axial dysfunction. The risk was also robustly increased with baseline tremor. This is of interest given recent reports of increased risk of dementia in patients with essential tremor.^{43⁴⁴}

When we treated MPS as a continuous variable, we found that with each one point increase in the Parkinsonian sign score, the risk of incident dementia increased by 15% (95% CI = 6% – 25%). Previous cohorts have found this value to be 4% (95% CI = 2% – 7%)³ and 8% (95% CI = 1% – 16%),⁸ values that are in the same general range as that which we report here.

A number of other baseline factors (e.g., education, family history of dementia, APOE-e4 status) have been associated with increased risk of dementia in the published literature.^{35–38} While one would expect in a given individual that the presence of MPS as well as one of these factors might increase the risk of dementia in an additive manner, we also examined here whether there was interaction between MPS and other baseline risk factors for dementia such that the presence of both together might greatly elevate the risk of developing dementia (i.e., the effect of both together is not simply additive). Identification of such interactions is potentially important as it would allow physicians to identify individuals with specific constellations of risk factors that place them at very high risk of developing dementia. However, we did not find any such interactions.

This study had limitations. Motor impairment and frailty are common in older people and are each associated with an increased risk of cognitive decline.⁴⁵ It is possible that frailty could be a confounder of the association between MPS and dementia. Nevertheless, in our adjusted analyses, we corrected for a number of factors that are contributors to frailty

(depression, diabetes mellitus, heart disease, stroke, and arthritis), suggesting that our results were not likely to be confounded in this way.

In summary, baseline MPS are now consistently being reported as a predictor of incident dementia. This further supports the view that these signs, although mild, may be a useful biomarker for future degenerative pathology.

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Table 1

Baseline characteristics of participants with baseline MPS vs. participants without baseline MPS

Characteristic	MPS N = 270	No MPS N = 1,581
Age in years ***	79.2 ± 7.4	75.6 ± 6.3
Female gender	168 (62.2%)	1,059 (67.0%)
Race		
White	89 (33.0%)	494 (31.2%)
African-American	86 (31.9%)	511 (32.3%)
Hispanic	92 (34.1%)	547 (34.6%)
Other	3 (1.1%)	29 (1.8%)
Education in years *	10.0 ± 4.6	10.8 ± 4.8
Smoker (ever)	120 (48.4%)	730 (49.3%)
Depressed	58 (21.6%)	291 (18.5%)
APOE-e4 positive	50 (22.9%)	370 (26.9%)
Hypertension	188 (69.6%)	1,051 (66.6%)
Diabetes mellitus **	67 (24.8%)	280 (17.7%)
Heart disease **	97 (35.9%)	415 (26.3%)
Stroke ***	64 (23.7%)	117 (7.4%)
Arthritis	146 (54.3%)	798 (50.6%)
Family history of dementia	59 (24.4%)	311 (21.6%)

*
p < 0.05**
p < 0.01***
p < 0.001 comparing MPS to no MPS.

For several variables, data were available on fewer than 1,851 participants. History of hypertension, diabetes, heart disease, stroke, and arthritis were by self-report.

Table 2

Baseline characteristics of participants who developed dementia vs. participants who did not develop dementia

Characteristic	Incident dementia N = 165	Not demented N = 1,686
Age in years ***	80.0 ± 7.2	75.7 ± 6.4
Female gender	111 (67.3%)	1,116 (66.2%)
Race ***		
White	31 (18.8%)	552 (32.7%)
African-American	45 (27.3%)	552 (32.7%)
Hispanic	87 (52.7%)	552 (32.7%)
Other	2 (1.2%)	30 (1.8%)
Education in years ***	7.5 ± 4.8	11.0 ± 4.6
Smoker (ever)	78 (48.8%)	772 (49.2%)
Depressed *	41 (25.2%)	308 (18.3%)
APOE-e4 positive	43 (31.4%)	377 (25.9%)
Hypertension	112 (67.9%)	1,127 (66.9%)
Diabetes mellitus *	42 (25.5%)	305 (18.1%)
Heart disease	48 (29.1%)	464 (27.5%)
Stroke ***	31 (18.8%)	150 (8.9%)
Arthritis	88 (53.3%)	856 (50.9%)
Family history of dementia	33 (21.4%)	337 (22.1%)

*
p < 0.05**
p < 0.01***
p < 0.001.

History of hypertension, diabetes, heart disease, stroke, and arthritis were by self-report.

Table 3

Baseline MPS subtypes and risk of dementia

MPS Subtype	Initial model* HR (95% CI), p value	Adjusted model** HR (95% CI), p value
Axial dysfunction	2.66 (1.68 – 4.21), p <0.001	2.45 (1.52 – 3.94), p <0.001
Tremor	2.21 (1.22 – 4.01), p = 0.009	2.38 (1.28 – 4.45), p = 0.006
Rigidity	1.50 (0.92 – 2.44), p = 0.11	1.16 (0.69 – 1.94), p = 0.58

* Cox model adjusted for age.

** Cox model adjusted for age, race, education, depression, diabetes mellitus, heart disease, stroke, and arthritis.

Table 4

Interactions between baseline MPS and other baseline risk factors for dementia

Interaction Terms	HR (95% CI), p value for interaction term*
MPS*Education	0.93 (0.48 – 1.81), p = 0.83
MPS*Gender	1.22 (0.59 – 2.53), p = 0.59
MPS*Hispanic Race	1.49 (0.79 – 2.83), p = 0.22
MPS*Family History of Dementia	0.66 (0.27 – 1.62), p = 0.36
MPS*Stroke	0.84 (0.37 – 1.90), p = 0.68
MPS*Diabetes Mellitus	0.67 (0.30 – 1.52), p = 0.34
MPS*Heart Disease	1.26 (0.61 – 2.60), p = 0.54
MPS*APOE-e4 positive	0.83 (0.34 – 2.05), p = 0.68

In each Cox proportional hazards model, we included age, MPS, the main term (e.g., education) and the interaction term (e.g., MPS*education).