

Published in final edited form as:

Arch Neurol. 2008 December ; 65(12): 1649–1654. doi:10.1001/archneurol.2008.504.

Quantitative Brain Measures in the Community-Dwelling Elderly with Mild Parkinsonian Signs

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Abstract

Background—Mild Parkinsonian signs (MPS) are a marker for incident dementia. MPS have been linked with cerebrovascular disease, which can be evaluated using magnetic resonance imaging (MRI). Also, if MPS are a marker for developing Alzheimer's type changes, hippocampal volume on MRI might be diminished among individuals with MPS.

Objective—To examine white matter hyperintensity (WMH) volume and total hippocampal volume in elderly with vs. without MPS.

Methods—Community-dwelling elderly in northern Manhattan had a neurological examination and brain MRI. WMH volume (derived on FLAIR-weighted MRI scans using a semi-automated thresholding approach) and total hippocampal volume (manually-derived) were expressed relative to total cranial volume.

Results—MPS were present in 111/666 (16.7%) participants. Relative WMH volume was larger in participants with vs. without MPS (1.70 ± 1.28 vs. 1.17 ± 1.18 , $p < 0.001$) and, in a multivariate logistic regression analysis adjusting for age, gender, years of education, ethnicity, and depression, relative WMH volume was associated with MPS (OR = 1.26, 95% CI = 1.08 – 1.47, $p = 0.004$). In both unadjusted and adjusted analyses, total relative hippocampal volume was similar in participants with vs. without MPS, regardless of cognitive status.

Conclusions—In this MRI study of the community-dwelling elderly, WMH volume was associated with MPS and total relative hippocampal volume was not. These data raise the possibility that vascular disease could play a role in the development of MPS.

Keywords

elderly; mild parkinsonian signs; magnetic resonance imaging; hippocampus; Alzheimer's disease; population; epidemiology; white matter hyperintensities

Introduction

Signs of tremor, rigidity, and bradykinesia are commonly found during the clinical examination of older people without known neurological disease.^{1, 2, 3, 4} It is unclear whether the emergence of these mild Parkinsonian signs (MPS) reflects the development of vascular pathology in the brain, the early development of degenerative (e.g., Alzheimer's or Lewy body) pathologies in the brain, or an age-associated decline in nigrostriatal dopaminergic activity.⁵

There is a growing literature linking MPS to vascular risk factors and vascular disease.⁵ In several studies, white matter hyperintensity (WMH) severity has been linked to impaired gait and balance in the elderly,^{6, 7} although MPS per se have not been studied in very much detail.⁶ If MPS are a marker for vascular disease, one could hypothesize that WMH volume would be greater among individuals with MPS.

Hippocampal volume is diminished in patients with early Alzheimer's disease (AD).^{8, 9} Pathological changes in the hippocampus are among the earliest manifestation of AD.¹⁰ MPS are associated with mild cognitive impairment (MCI)¹¹ and are a marker for the subsequent development of incident dementia.^{2, 12} If MPS are indeed a marker for developing Alzheimer's type changes in the brain, one could hypothesize that hippocampal volume would be diminished among individuals with MPS.

The current study was conducted in community-dwelling older people living in Washington Heights-Inwood, northern Manhattan, New York. In 2003, we began systematically acquiring structural magnetic resonance imaging (MRI) scans on active, non-demented participants in the study cohort. The purpose of the current analyses was to test the hypotheses that (1) WMH volume is greater among the elderly with MPS when compared to their counterparts without MPS, and (2) total hippocampal volume is reduced among the elderly with MPS when compared to their counterparts without MPS.

Methods

Study Population and Final Sample

2,776 individuals participated in a prospective study of aging and dementia in Medicare-eligible northern Manhattan residents, age 65 years and older (Washington/Hamilton Heights-Inwood Columbia Aging Project: WHICAP II), as described elsewhere.^{13, 14} Recruitment, informed consent and study procedures were approved by the Columbia University Institutional Review Board.

The imaging protocol was concurrent with the second follow-up visit of the WHICAP II cohort (n = 2,113).¹⁴ There were 769 participants who received MRI scans; eligibility and participation has been documented elsewhere.¹⁴ We further excluded 50 participants with incomplete MRI data, 19 with incomplete neurological examination data, and 34 with incomplete neuropsychological test data. Of the remaining 666 participants in the final sample,

none had Parkinson's disease (PD) or Parkinson Plus syndrome, as have been defined previously.¹¹

Study Evaluation

Interview—A trained research assistant collected demographic information and administered a structured interview of health history (e.g., hypertension, stroke, diabetes mellitus, each by self-report).

Neurological Examination—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).¹¹ The ten-item version of the motor portion of the 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.¹¹ 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 movement disorder neurologist's ratings (E.D.L.) was 79%.¹¹

As in previous analyses,¹¹ 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. MPS was stratified into three subtypes (axial function [changes in speech, facial expression, changes in posture, and axial bradykinesia], rigidity, tremor) based on a factor analysis.¹⁵ 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 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 rating ≥ 2 . Tremor was considered present when the participants had a UPDRS rest tremor rating = 1.¹¹

Neuropsychological Battery—As previously described,¹⁶ all participants underwent a standardized neuropsychological battery¹⁷ and were considered demented if they met established criteria.¹⁸ Participants with MCI were stratified into those with (1) isolated impairment in memory or impairment in memory as well as one or more other cognitive domains (MCI+M) or (2) no impairment in memory but impairment in one or more other cognitive domains (MCI-M).

Depressive symptoms were assessed and rated with a 9-item version of the Center for Epidemiological Study Depression (CESD) scale.¹⁹ Based on a previously established cut point,²⁰ a score ≥ 4 was coded as depressed.

MRI Protocol

Acquisition—Scan acquisition was performed on a 1.5T Philips Intera scanner at Columbia University Medical Center and transferred electronically to the University of California at Davis for morphometric analysis in the Imaging of Dementia and Aging Laboratory.¹⁴ T1-weighted images acquired in the axial plane and resectioned coronally were used to quantify hippocampus volume (TR=20 ms, TE = 2.1 ms, FOV 240 cm, 256×160 matrix with 1.3 mm slice thickness). For measures of total cranial volume and WMH volume, fluid attenuated inverse recovery (FLAIR) weighted images (TR=11,000 ms, TE=144.0 ms, 2800 inversion time, FOV 25 cm, 2 nex, 256×192 matrix with 3 mm slice thickness) were acquired in the axial orientation.

Quantification of total relative hippocampal volume, total cranial volume, and relative WMH volume—User operated image analysis was performed on a Sun Microsystems Ultra 5 workstation using the Quantum 6.2 package. Hippocampal volumes were measured by manual tracing as described previously.¹⁴ Intra-rater reliability determined for both right and left hippocampus using this method was good with intraclass correlation coefficients of 0.98 for right hippocampus and 0.96 for left hippocampus. For the current analyses, we reported total relative hippocampal volume (i.e., total hippocampal volume expressed as a percentage of total cranial volume). In this dataset, delayed recall²¹ was associated with total relative hippocampal volume, even after adjusting for age (beta = 5.20, p = 0.003).

Total cranial and WMH volumes were derived on FLAIR-weighted images following a two-step process, as previously described.^{14, 22, 23} First, an operator manually traced the dura mater within the cranial vault, including the middle cranial fossa but not the posterior fossa and cerebellum. Total intracranial volume was defined as the number of voxels contained within the manual tracings, multiplied by the voxel dimensions and slice thickness. Nonuniformities in image intensity were removed²⁴ and two Gaussian probability functions, representing brain matter and cerebrospinal fluid (CSF), were fitted to the skull-stripped image. Once brain matter was isolated, a single Gaussian distribution was fitted to image data and a segmentation threshold for WMH was set *a priori* at 3.5 SDs in pixel intensity above the mean of the fitted distribution of brain matter. Erosion of two exterior image pixels was applied to the brain matter image before modeling to remove partial volume effects and ventricular ependyma on WMH determination. WMH volume was calculated as the sum of the remaining voxels multiplied by the voxel dimensions and slice thickness. For the current analyses, we reported total relative WMH volume (i.e., total WMH volume expressed as a percentage of total cranial volume).

MRI Infarcts—As previously described,²⁵ the presence or absence of cerebral infarction on MRI was determined for all subjects from the size, location and imaging characteristics of the lesion. Only lesions 3 mm or larger qualified for classification as cerebral infarcts.

Statistical Analyses—Analyses were conducted in SPSS Version 15.0. Among the participants with MPS, quartiles were established based on the Parkinsonian sign score (no MPS, MPS lowest quartile [Parkinsonian sign score = 1], MPS second quartile [Parkinsonian sign score = 2], MPS third quartile [Parkinsonian sign score = 3 – 6], MPS highest quartile [Parkinsonian sign score ≥ 7]). In regression analyses, we began with unadjusted models and then considered a number of potential confounders if they were associated with the main variables in univariate analyses. Because relative WMH volume was not normally distributed, univariate tests were non-parametric (e.g., Mann Whitney) and this variable was log transformed in linear regression analyses.

Results

MPS

There were 666 participants. The Parkinsonian sign score was ≥ 1 in 154 (23.1%) of 666 participants, and 111 (16.7%) of 666 participants had MPS. MPS was associated with older age, ethnicity, fewer years of education, and higher prevalence of self-reported stroke (Table 1). Dementia was more prevalent in participants with vs. without MPS (p < 0.001, Table 1), and 19 (42.2%) of 45 participants with dementia vs. 73 (15.7%) of 466 cognitively normal (i.e., without dementia or MCI) participants had MPS (chi-square = 19.61, p < 0.001).

The 666 participants included 466 (70.0%) cognitively normal, 68 (10.2%) with MC-M, 87 (13.1%) with MCI+M, and 45 (6.7%) demented.

The time between the clinical examination and MRI was short (mean = 1.8 ± 4.9 , median = 0 months) and was not correlated with relative WMH volume or total relative hippocampal volume.

Relative WMH Volume

Correlates of relative WMH volume are shown (Table 2). In a multivariate linear regression model, log relative WMH volume was associated with age ($\beta = 0.04$, $p < 0.001$) and ethnicity ($\beta = 0.16$, $p = 0.002$) but not with gender, years of education, or depression. Relative WMH volume was larger in demented vs. cognitively normal participants (1.75 ± 1.41 vs. 1.15 ± 1.09 , Mann Whitney $z = 3.44$, $p = 0.001$).

Relative WMH volume was larger in participants with vs. those without MPS (1.70 ± 1.28 [N = 111] vs. 1.17 ± 1.18 [N = 555], Mann Whitney $z = 4.60$, $p < 0.001$). When we excluded 69 participants who reporting having had a stroke, relative WMH volume remained larger in participants with vs. without MPS (1.63 ± 1.25 vs. 1.16 ± 1.17 , Mann Whitney $z = 3.90$, $p < 0.001$). When we further excluded 171 participants who had stroke on MRI, this difference persisted (1.32 ± 1.15 vs. 0.99 ± 0.90 , Mann Whitney $z = 2.04$, $p = 0.04$). In a multivariate logistic regression model, including all participants and adjusting for age, gender, years of education, ethnicity, and depression, relative WMH volume was associated with MPS (dependent variable): OR = 1.26, 95% CI = 1.08 – 1.47, $p = 0.004$.

In each of the four cognitive status strata, relative WMH volume was larger in participants with vs. without MPS, although in both unadjusted and adjusted analyses, the difference reached significance only in cognitively normal participants (OR = 1.27, 95% CI = 1.03 – 1.55, $p = 0.02$, Table 3). We hypothesized that basal ganglia infarction might be associated with MPS. However, the proportion of participants with MPS who had basal ganglia infarcts by MRI was not significantly higher than the proportion of participants without MPS who had these infarcts (9 [8.1%] vs. 29 [5.2%], chi-square = 1.43, $p = 0.23$).

In the 466 cognitively normal participants, MPS were further stratified into quartiles. Relative WMH volume was associated with MPS quartile: 1.08 ± 1.07 (no MPS), 1.30 ± 0.98 (lowest MPS quartile), 1.40 ± 1.26 (second MPS quartile), 1.41 ± 1.12 (third MPS quartile), and 2.28 ± 1.14 (highest MPS quartile) (Kruskal-Wallis chi-square = 19.19, $p = 0.001$, and in a linear regression model, MPS quartile [independent variable] was associated with log relative WMH volume [$\beta = 0.17$, $p < 0.001$]). Among the 466 cognitively normal participants, MPS were stratified into three subtypes (axial function, rigidity, and tremor). Relative WMH volume was larger in participants with vs. without axial dysfunction (1.50 ± 1.15 vs. 1.12 ± 1.08 , Mann Whitney $z = 2.40$, $p = 0.016$), with vs. without rigidity (1.53 ± 1.10 vs. 1.11 ± 1.08 , Mann Whitney $z = 2.98$, $p = 0.003$), and with vs. without tremor (1.64 ± 1.17 vs. 1.13 ± 1.08 , Mann Whitney $z = 2.45$, $p = 0.01$). In multivariate logistic regression models, adjusting for age, gender, years of education, ethnicity, and depression, the association between relative WMH volume and MPS subtype (dependent variable) was similar for each MPS subtype (OR = 1.19, 95% CI = 0.91 – 1.57, $p = 0.21$ [axial function]; OR = 1.24, 95% CI = 0.98 – 1.56, $p = 0.07$ [rigidity]; OR = 1.30, 95% CI = 0.96 – 1.76, $p = 0.09$ [tremor]).

Total Relative Hippocampal Volume

The correlates of total relative hippocampal volume are shown (Table 2). In a multivariate linear regression model, total relative hippocampal volume was not associated with age, gender, years of education, ethnicity or depression. Total relative hippocampal volume was smaller in the 45 demented vs. 466 cognitively normal participants (0.25 ± 0.06 vs. 0.29 ± 0.06 , $t = 4.14$, $p < 0.001$).

In each of the four cognitive status strata, in both unadjusted analyses and in adjusted logistic regression analyses, total relative hippocampal volume was similar in participants with vs. without MPS (Table 3). In each of the four cognitive status strata, there was no correlation between total relative hippocampal volume and Parkinsonian sign score: $r = 0.06$, $p = 0.22$ (cognitively normal); $r = 0.05$, $p = 0.67$ (MCI-M); $r = -0.10$, $p = 0.38$ (MCI+M); and $r = 0.13$, $p = 0.39$ (demented).

Among the 466 cognitively normal participants, MPS were further stratified into quartiles. There was no association between MPS quartile and total relative hippocampal volume: 0.29 ± 0.06 (no MPS), 0.28 ± 0.07 (lowest MPS quartile), 0.30 ± 0.06 (second MPS quartile), 0.29 ± 0.06 (third MPS quartile), and 0.31 ± 0.06 (highest MPS quartile) (ANOVA $F = 0.49$, $p = 0.75$). MPS were stratified into three subtypes (axial function, rigidity, and tremor). Total relative hippocampal volume was similar in participants with vs. without axial dysfunction (0.29 ± 0.06 vs. 0.29 ± 0.06 , $t = 0.22$, $p = 0.83$), with vs. without rigidity (0.29 ± 0.06 vs. 0.30 ± 0.06 , $t = 0.63$, $p = 0.18$), and with vs. without tremor (0.29 ± 0.06 vs. 0.30 ± 0.05 , $t = 0.28$, $p = 0.78$). In multivariate logistic regression analyses that adjusted for age in years, gender, years of education, ethnicity, depression, and stroke, total relative hippocampal volume was not associated with each MPS subtype (dependent variables in different models).

Discussion

We found a robust association between higher relative WMH volume and presence of MPS. Furthermore, there was a dosing effect whereby step-wise increases in relative WMH volume were observed in higher MPS quartiles. There have been several epidemiological studies of elderly persons with MPS, demonstrating associations between vascular risk factors or vascular disease and MPS.²⁶⁻²⁸ In a sizable number of MRI studies, subcortical WMH have been linked with impaired gait and balance in the elderly,^{6, 7, 29} although MPS per se and their relationship to these hyperintensities have not been studied in very much detail.⁶ Hence, this study extends prior research by linking WMH to different kinds of motor dysfunction. Further along the spectrum of parkinsonism than MPS (i.e., a more severe syndrome) is vascular parkinsonism, which also has as its underpinnings, vascular lesions.³⁰ Our MRI data further raise the possibility that vascular disease could play a role in the development of MPS. However, this conclusion should be reached with caution. While WMH are associated with cerebrovascular mechanisms, one cannot necessarily equate the two.

The links between MPS in the non-demented elderly and the development of AD are based on epidemiological evidence. Longitudinal studies^{2, 12, 31} have demonstrated that individuals with MPS are more likely than are their counterparts without MPS to develop dementia. The majority of these develop AD rather than other forms of dementia.^{2, 12} Limited postmortem evidence also suggests a possible link between Alzheimer's type pathology and one manifestation of MPS, gait disturbance. In a study of non-demented deceased persons in the Religious Orders Study,³² the number of neurofibrillary tangles in the substantia nigra was related to gait disturbance. To further examine the links between MPS and AD, we examined total relative hippocampal volume in community-dwelling elderly with vs. without MPS. We did not find an association between total relative hippocampal volume and MPS or any of the MPS subtypes. This finding seems to argue against the notion that MPS themselves are a manifestation of early AD. However, these findings should be approached with caution because hippocampal volume is affected by factors other than AD, AD pathology affects many brain regions besides the hippocampus, and the hippocampus is not generally thought to play a role in MPS.

We did not find an association between hippocampal volume and age. There is sizable literature on the relationship between hippocampal volume and age, with contradictory results. In some studies, there is an aging effect,³³⁻³⁵ whereas in others, there is not.³⁶⁻³⁸

The strengths of this study include the population-based design and the large sample size. This is also the first attempt, to our knowledge, to examine structural changes in the hippocampus in the non-demented elderly with MPS. The study's limitations include the cross-sectional design, preventing us from being able to examine associations between clinical course and longitudinal imaging changes. Second, we did not perform postmortem examinations and were not able to correlate our findings with findings from microscopic pathologic studies. Finally, as reported previously,¹⁴ individuals who refused participation in the MRI study were a year older and more likely to be women and White, which may have introduced some biases. In our analyses, we adjusted for these demographic factors.

In summary, in this study of the community-dwelling elderly, we noted that relative WMH volume was associated with MPS and total relative hippocampal volume was not associated with MPS. These data raise the possibility that vascular disease could play a role in the development of MPS.

Acknowledgements

Work was supported by Federal Grants NIH P01 AG07232 and R01 NS42859.

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Table 1

Comparison of participants with MPS vs. without MPS

	MPS (N = 111)	No MPS (N = 555)	Significance (p)
Age in years	83.2 ± 5.8	79.7 ± 5.4	<0.001 ^a
Women	71 (64.0%)	377 (67.9%)	0.42 ^b
Ethnicity			0.01 ^b
White	18 (16.2%)	166 (29.9%)	
African-American	48 (43.2%)	188 (33.9%)	
Hispanic	45 (40.5%)	201 (36.2%)	
Years of education	9.3 ± 4.9	10.9 ± 4.8	0.002 ^a
Depressed	14 (12.6%)	69 (12.4%)	0.96 ^b
Self-reported Stroke	22 (19.8%)	47 (8.5%)	<0.001 ^b
Hypertension	73 (65.8%)	378 (68.1%)	0.63 ^b
Diabetes mellitus	25 (22.5%)	123 (22.2%)	0.93 ^b
Demented	19 (17.1%)	26 (4.7%)	<0.001 ^b

^a t test^b Chi-square test

Table 2

Correlates of relative WMH volume and total relative hippocampal volume

	Relative WMH volume	Total relative hippocampal volume
Age in years	0.22 *** ^a	r = -0.01
Gender		
Men	1.13 ± 1.06	0.28 ± 0.06
Women	1.33 ± 1.28	0.29 ± 0.06
Ethnicity		
White	0.94 ± 0.94 *** ^b	0.29 ± 0.06
African-American	1.50 ± 1.45	0.29 ± 0.06
Hispanic	1.28 ± 1.09	0.29 ± 0.06
Years of education	-0.11 *** ^a	r = 0.03
Depressed		
Yes	1.39 ± 1.09 * ^c	0.29 ± 0.07
No	1.24 ± 1.23	0.29 ± 0.06
Self-reported stroke		
Yes	1.58 ± 1.34 * ^c	0.30 ± 0.06
No	1.22 ± 1.19	0.29 ± 0.06
Self-reported hypertension		
Yes	1.33 ± 1.27 * ^c	0.29 ± 0.06
No	1.11 ± 1.06	0.29 ± 0.06
Self-reported diabetes mellitus		
Yes	1.21 ± 1.04	0.29 ± 0.06
No	1.28 ± 1.26	0.29 ± 0.06
Demented		
Yes	1.75 ± 1.41 ** ^c	0.25 ± 0.06 *** ^d
No (cognitively normal)	1.15 ± 1.09	0.29 ± 0.06

* p < 0.05

** p < 0.01

*** p < 0.001.

^a Spearman's correlation coefficient.^b Kruskal-Wallis test.^c Mann Whitney test.^d t test.

Table 3

Total relative hippocampal volume and relative WMI volume by MPS in each cognitive status stratum

	Cognitively normal (N = 466)	MCI – M (N = 68)	MCI + M (N = 87)	Demented (N = 45)
Relative WMH Volume ¹				
No MPS	1.08 ± 1.07	1.35 ± 1.60	1.38 ± 1.20	1.55 ± 1.41
MPS	1.52 ± 1.15**	2.56 ± 1.84*	1.89 ± 1.44	2.02 ± 1.40
Total Relative Hippocampal Volume ²				
No MPS	0.29 ± 0.06	0.30 ± 0.06	0.29 ± 0.06	0.25 ± 0.06
MPS	0.30 ± 0.06	0.29 ± 0.05	0.28 ± 0.06	0.26 ± 0.06

* p < 0.05

** p < 0.001 (comparing no MPS to MPS using Mann Whitney test).

¹ Within each cognitive status stratum, in a multivariate logistic regression model that adjusted for age, gender, years of education, ethnicity, and depression, the association between relative WMH volume and MPS (dependent variable) was as follows: OR = 1.27, 95% CI = 1.03 – 1.55, p = 0.02 (cognitively normal); OR = 1.34, 95% CI = 0.82 – 2.21, p = 0.24 (MCI – M); OR = 1.53, 95% CI = 0.91 – 2.57, p = 0.11 (MCI + M); and OR = 1.21, 95% CI = 0.66 – 2.20, p = 0.54 (demented).

² Within each cognitive status stratum, in a multivariate logistic regression model that adjusted for age, gender, years of education, ethnicity, depression and stroke, total relative hippocampal volume was not associated with MPS (dependent variable): p = 0.42 (cognitively normal); p = 0.99 (MCI – M); p = 0.97 (MCI + M); and p = 0.66 (demented).