

History of Vascular Disease and Mild Parkinsonian Signs in Community-Dwelling Elderly Individuals

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Background: Mild parkinsonian signs (MPS) are commonly found during the clinical examination of older people. These signs could reflect the accumulation of vascular pathological changes in the brain. If the etiology were vascular, one could hypothesize that individuals with MPS would be more likely to have systemic vascular disease than would their counterparts without these signs.

Objectives: To examine whether MPS are associated with a history of vascular disease and whether certain MPS (rigidity, changes in axial function) are more strongly associated with a history of vascular disease than are other MPS (tremor).

Methods: Evaluation of older people without dementia in Washington Heights-Inwood, northern Manhattan, NY. The presence of vascular diseases was assessed with a structured health interview.

Results: Mild parkinsonian signs were present in 375 (16.4%) of 2286 participants without dementia. Diabe-

tes mellitus, heart disease, peripheral vascular disease, and stroke were more prevalent in participants with MPS than without MPS, whereas nonvascular diseases (cancer, thyroid disease) were not. In a logistic regression analysis that adjusted for age, sex, education, and depressive symptoms, the number of vascular diseases was associated with MPS (odds ratio, 1.31 [95% confidence interval, 1.18-1.46]; $P < .001$). The combination of diabetes mellitus and heart disease increased the odds of MPS by 70% and the combination of these with stroke increased the odds by 332%.

Conclusions: The presence of MPS in elderly individuals might reflect, in part, the accumulation of vascular pathological changes in the basal ganglia or white matter regions caused by preventable vascular diseases. Prospective and pathological studies are needed to further explore this finding.

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PARKINSONIAN-LIKE SIGNS (RIGIDITY, bradykinesia) are commonly found during the clinical examination of older people who do not have known neurological disease.¹⁻⁴ It is unclear whether these mild parkinsonian signs (MPS) reflect an age-associated decline in nigrostriatal dopaminergic activity, the early development of degenerative abnormalities in the basal ganglia, or the accumulation of vascular pathological changes in the basal ganglia or subcortical (white matter) regions.¹⁻⁵ There is some evidence to support a role for vascular pathological changes, particularly in the development of certain MPS (ie, rigidity and gait disturbance).⁶⁻⁹ Vascular pathological changes in the brain (subcortical white matter changes, lacunar infarcts) often occur in the setting of systemic vascular disease or risk factors for such disease (eg, hypertension, diabetes mellitus). If the etiology of MPS were vascular, one

might hypothesize that individuals with MPS would be more likely to have evidence of systemic vascular disease when compared with their counterparts without these signs.

The current study was conducted in community-dwelling older people without dementia living in Washington Heights-Inwood, northern Manhattan, NY, who had an examination between 1999 and 2001. The goal of this report was to examine whether MPS are associated with a history of vascular disease and whether certain MPS (rigidity, changes in axial function) are more strongly associated with a history of vascular disease than other MPS (tremor).

METHODS

STUDY POPULATION

Study participants were drawn by random sampling of healthy Medicare beneficiaries who were 65 years and older and resided

within a geographically defined area of northern Manhattan.¹⁰ The cohort represents a combination of continuing members of a cohort originally recruited in 1992 and members of a new cohort recruited between 1999 and 2001; approximately one quarter of the sample was from the original 1992 cohort and three quarters, from the new cohort. Recruitment of all participants was initially achieved by contacting a stratified random sample of 50% of all persons 65 years and older obtained from the Health Care Finance Administration (Center for Medicare Services).¹⁰ As of July 1, 2004, data were available on 2776 participants who were evaluated between 1999 and 2001 (for the original 1992 cohort, this represented their third follow-up assessment, and for the new cohort, this represented their baseline assessment).¹⁰ The mean (SD) age of the 2776 participants was 78.2 (7.1) years; 1886 (67.9%) were women and 1098 (39.6%) were Hispanic. Their mean (SD) education was 9.9 (4.9) years.

A trained research assistant administered a structured interview of health. This included demographic questions and questions on the presence or absence (either currently or in the past) of hypertension, diabetes mellitus, heart disease (including myocardial infarction, congestive heart failure, or other heart conditions), peripheral vascular disease, stroke, chronic obstructive pulmonary disease, thyroid disease, liver disease, renal disease, peptic ulcer disease, cancer, arthritis, head injury with loss of consciousness, and seizures. Systolic and diastolic blood pressures were measured by the assistant. Each participant also underwent a standardized neurological examination, which included an abbreviated (10-item) version of the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS).¹¹ We assigned a diagnosis of Parkinson disease (PD) or Parkinson plus syndrome based on research criteria¹² and participants were considered to have PD or Parkinson plus syndrome if (1) they had previously received a diagnosis of PD or Parkinson plus syndrome, or (2) they had 2 or more cardinal signs of parkinsonism on the standardized neurological examination. Cardinal signs were rest tremor, rigidity, bradykinesia, and changes in posture. For the diagnosis of PD or Parkinson plus syndrome, a cardinal sign was considered to be present when 1 UPDRS rating was 2 or higher. There were 8 participants with 1 cardinal sign and either (1) increased tone in the setting of upper motor neuron signs (eg, participants with a history of a symptomatic stroke with residual weakness or participants with multiple sclerosis) or (2) stooped posture due to severe musculoskeletal problems (eg, kyphosis, scoliosis); they were not diagnosed with PD. Thirty-two participants (1.2%) had a diagnosis of PD or Parkinson plus syndrome, which is consistent with a prevalence of PD that has been reported for persons 65 years and older in northern Manhattan.¹³

We excluded 490 participants for the following reasons. The 32 participants with PD or Parkinson plus syndrome were excluded because our intention was to study a community population of older people without these diseases. We also excluded 330 participants because they had dementia; this would lessen the validity of their response to questions about medical conditions. Participants with incomplete UPDRS data (n=128) were excluded as well. Parkinsonian signs can result from the use of neuroleptic medications, but none of the remaining participants were taking these. The final sample, 2286 participants, had a mean (SD) age of 77.2 (6.6) years and a mean (SD) education of 10.3 (4.8) years; 1535 (67.1%) were women and 844 (36.9%) were Hispanic. The study was approved by our institution's internal review board and written consent was obtained from all participants.

NEUROLOGICAL EVALUATION

The 10-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.¹⁰ Each of the 10 items was rated from 0 to 4. The general medical doctors who administered the modified motor portion of the UPDRS were trained using a structured protocol, as documented elsewhere.¹⁰

As in previous analyses,¹⁰ MPS were defined as present when any 1 of the following conditions was met: (1) 2 or more UPDRS ratings of 1, (2) 1 UPDRS rating of 2 or higher, or (3) a UPDRS rest tremor rating of 1. Based on a factor analysis, MPS were stratified into 3 MPS subscores: axial function (changes in speech, facial expression, changes in posture, and axial bradykinesia), rigidity, and tremor.^{10,14} An abnormality in axial function was considered present when the participants had either (1) UPDRS ratings of 1 in 2 or more items or (2) 1 UPDRS rating of 2 or higher. Rigidity was considered present when the participants had either (1) UPDRS ratings of 1 in 2 or more items or (2) 1 UPDRS rating of 2 or higher. Tremor was considered present when the participants had a UPDRS rest tremor rating of 1.¹⁰

All participants underwent a standardized neuropsychological battery.¹⁵ The neuropsychological battery was designed to assess cognitive functions that are typically affected in dementia¹⁵ and included measures of learning and memory, orientation, abstract reasoning, language, and visuospatial ability. Participants were considered to have dementia if they met established criteria.¹⁶ As noted earlier, the 330 participants who met inclusion criteria for dementia were excluded. A designation of mild cognitive impairment required (1) objective impairment in at least 1 of 4 cognitive domains (memory, executive function, language, and visuospatial) based on performance on the neuropsychological test battery and a 1.5-SD cutoff for a domain score using normative corrections for age, years of education, ethnicity, and sex, (2) a subjective complaint of memory impairment, and (3) absence of functional impairment, according to published criteria.^{17,18}

Depressive symptoms were assessed and rated with a 9-item version of the Center for Epidemiologic Studies Depression (CES-D) Scale,¹⁹ in which individuals reported symptoms of depression (range, 0 [no depressive symptoms] to 9 [maximal depressive symptoms]).

STATISTICAL ANALYSES

Analyses were conducted in SPSS version 11.0. Differences in categorical variables were assessed with χ^2 tests and differences in continuous variables, with either *t* tests or analysis of variance. We grouped diseases into vascular diseases (ie, diseases that are often associated with pathological vascular changes: hypertension, diabetes mellitus, heart disease, peripheral vascular disease, stroke) vs nonvascular diseases (eg, cancer, chronic obstructive pulmonary disease, thyroid disease).

In unadjusted and then adjusted logistic regression analyses, we examined the associations between MPS (dependent variable) and reported vascular diseases, with each vascular disease being an independent variable in a separate logistic regression model. This resulted in odds ratios (ORs) with 95% confidence intervals (CIs). In unadjusted and then adjusted logistic regression analyses, we examined the associations between different MPS subscores (changes in axial function, rigidity, tremor) and reported vascular diseases, with each vascular disease being an independent variable in a separate logistic regression model. In adjusted analyses, we considered the fol-

lowing confounders based on our own analyses in this data set as well as published literature^{1-4,10}: age in years, sex, years of education, CES-D score, and history of arthritis. In 1 set of analyses, we defined MPS as being present when any UPDRS rating was 1 or higher and absent when all UPDRS ratings were 0; the goal of these analyses was to increase power for association. In several analyses, we excluded participants with reported stroke because stroke can result in spasticity, which on examination, can be difficult to distinguish from increased tone in the setting of rigidity. For other analyses, the number of reported vascular diseases was summed. In a secondary analysis, we defined hypertension based on history and examination (reported hypertension by history or a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg).

RESULTS

Mild parkinsonian signs were present in 375 (16.4%) of 2286 participants without dementia. Mild parkinsonian signs included changes in axial function (168 participants [7.3%]), rigidity (221 [9.7%]), and tremor (93 [4.1%]). The 375 participants with MPS were older and had fewer years of education than the 1911 participants without MPS (**Table 1**).

Participants with MPS differed from their counterparts without MPS in terms of the proportions with vascular diseases, even after excluding participants with stroke; the 2 groups did not differ with respect to the proportions with most nonvascular diseases (**Table 2**). In logistic regression analyses (**Table 3**), we examined the associations between MPS (dependent variable) and vascular diseases, with each vascular disease being an independent variable in a separate logistic regression model. Mild parkinsonian signs were associated with diabetes mellitus, heart disease, peripheral vascular disease, and stroke; after excluding participants with stroke, the results were similar. The combination of diabetes mellitus and heart disease (vs neither) was associated with an 86% increased odds of MPS (OR, 1.86 [95% CI, 1.23-2.80]; $P = .003$), and the combination of diabetes mellitus, heart disease, and stroke (vs none of these) was associated with a 450% increase in odds of MPS (OR, 4.50 [95% CI, 2.07-9.77]; $P < .001$) in unadjusted models. In a logistic regression analysis that adjusted for age, sex, education, CES-D score, and arthritis, the results were similar; the combination of diabetes mellitus and heart disease (vs neither) was associated with a 70% increased odds of MPS (OR, 1.70 [95% CI, 1.10-2.62]; $P = .02$), and the combination of diabetes mellitus, heart disease, and stroke (vs none of these) was associated with a 332% increase in odds of MPS (OR, 3.32 [95% CI, 1.47-7.52]; $P = .004$).

The number of vascular diseases was higher in participants with MPS compared with those without MPS (mean [SD], 1.61 [1.10] vs 1.25 [1.02]; $P < .001$), even after excluding participants with stroke (mean [SD], 1.37 [0.99] vs 1.15 [0.93]; $P < .001$). In a logistic regression analysis that adjusted for age, sex, education, CES-D score, and arthritis, the number of vascular diseases was associated with MPS (OR, 1.31 [1.18-1.46]; $P < .001$) (ie, for each reported vascular disease, the odds of having MPS increased by 31%). In this model, the OR for age was 1.08 (95% CI, 1.06-1.10) ($P < .001$). In an additional logistic

Table 1. Demographic and Clinical Characteristics of 2286 Participants Stratified by Presence or Absence of Mild Parkinsonian Signs (MPS)

Characteristic	MPS (n = 375)	No MPS (n = 1911)
Age, y, mean (SD)	80.2 (7.0)*	76.4 (6.4)
Female, No. (%)	240 (64.0)	1295 (67.8)
Ethnicity, No. (%)		
Non-Hispanic white	120 (32.0)	563 (29.5)
Non-Hispanic African American	121 (32.3)	605 (31.7)
Hispanic	130 (34.7)	714 (37.4)
Other	4 (1.1)	29 (1.5)
Education, y, mean (SD)	9.8 (4.7)†	10.5 (4.8)
CES-D score, mean (SD)	2.9 (1.5)†	2.7 (1.4)
Mild cognitive impairment, No. (%)‡	114 (30.9)	494 (26.5)
Cigarette smoker, No. (%)	45 (12.0)	196 (10.3)

Abbreviation: CES-D, Center for Epidemiologic Studies Depression Scale.

* $P < .001$.

† $P < .05$.

‡Data were missing on 56 participants.

regression analysis that adjusted for age, sex, education, CES-D score, and arthritis and that excluded all participants with stroke and mild cognitive impairment, the number of vascular diseases was associated with MPS (OR, 1.23 [95% CI, 1.05-1.45]; $P = .01$).

The number of nonvascular diseases was similar in participants with MPS compared with those without MPS (mean [SD], 1.04 [0.86] vs 1.01 [0.92]; $P = .49$). In an adjusted logistic regression analysis, the number of nonvascular diseases was not associated with MPS (OR, 0.96 [95% CI, 0.81-1.14]; $P = .64$).

A similar proportion of participants with vs those without MPS had a history of hypertension (Table 2). In a secondary analysis, we defined hypertension based on history and examination; hypertension was present in 315 (84.0%) of 375 participants with MPS vs 1506 participants (78.8%) without MPS ($\chi^2 = 5.22$; $P = .02$).

In adjusted logistic regression analyses, we examined the associations between different MPS subscores (changes in axial function, rigidity, tremor) and the number of reported vascular and nonvascular diseases; the number of reported vascular diseases was most strongly associated with rigidity (**Table 4**).

COMMENT

Vascular diseases were more common in community-dwelling elderly individuals with MPS compared with those without MPS, and in adjusted analyses, for each reported vascular disease, the odds of having MPS increased by 31%. The presence of vascular disease was most strongly associated with the presence of rigidity on examination.

These results suggest that the presence of MPS in elderly individuals might reflect, at least in part, the consequences of systemic vascular disease on the brain. The most likely mechanism is the accumulation of vascular pathological changes in either the basal ganglia or subcortical white matter regions (ie, the possible disruption of neural connections between the frontal cortex,

Table 2. Presence or Absence of Vascular vs Nonvascular Diseases in Participants Stratified by Presence or Absence of Mild Parkinsonian Signs (MPS)

	All Participants, No. (%)		Excluding Participants With Stroke, No. (%)	
	MPS (n = 375)	No MPS (n = 1911)	MPS (n = 305)	No MPS (n = 1790)
Vascular diseases				
Hypertension	252 (67.2)	1188 (62.2)	194 (63.6)	1094 (61.1)
Diabetes mellitus	83 (22.3)*	336 (17.7)	66 (21.8)*	306 (17.2)
Heart disease	128 (34.1)†	487 (25.5)	98 (32.1)†	428 (23.9)
Peripheral vascular disease	68 (18.1)*	258 (13.5)	57 (18.7)†	226 (12.6)
Stroke	70 (18.9)‡	121 (6.4)	0	0
Nonvascular diseases				
Chronic obstructive pulmonary disease	40 (10.7)	197 (10.3)	37 (12.1)	180 (10.1)
Thyroid disease	40 (10.7)	182 (9.5)	30 (9.8)	169 (9.4)
Liver disease	2 (0.5)	35 (1.8)	2 (0.7)	30 (1.7)
Renal disease	4 (1.1)	23 (1.2)	3 (1.0)	21 (1.2)
Peptic ulcer disease	36 (9.6)	203 (10.6)	29 (9.5)	177 (9.9)
Cancer	37 (9.9)	205 (10.7)	29 (9.5)	184 (10.3)
Arthritis	219 (58.4)*	1007 (52.7)	180 (59.0)*	943 (52.7)
Head injury with loss of consciousness	9 (2.4)	57 (3.0)	6 (2.0)	53 (3.0)
Seizures	5 (1.3)	24 (1.3)	4 (1.3)	16 (0.9)

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

Table 3. Associations Between Vascular Diseases and Mild Parkinsonian Signs (MPS) in Logistic Regression Analyses*

Vascular Disease	Unadjusted†		Adjusted‡		Adjusted and Excluding Participants With Stroke‡	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Hypertension	1.24 (0.98-1.57); 1.24 (1.02-1.51)	.07; .03	1.17 (0.91-1.50)	.21	1.06 (0.81-1.39)	.65
Diabetes mellitus	1.34 (1.02-1.76); 1.34 (1.06-1.68)	.04; .01	1.37 (1.03-1.82)	.03	1.34 (0.98-1.84)	.07
Heart disease	1.52 (1.20-1.92); 1.64 (1.34-2.00)	.001; <.001	1.33 (1.04-1.70)	.02	1.35 (1.02-1.77)	.04
Peripheral vascular disease	1.42 (1.06-1.90); 1.61 (1.26-2.06)	.02; <.001	1.29 (0.95-1.76)	.08	1.45 (1.03-2.03)	.03
Stroke	3.41 (2.48-4.69); 3.39 (2.51-4.58)	<.001; <.001	3.30 (2.37-4.59)	<.001	NA	

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; NA, not applicable; OR, odds ratio; UPDRS, Unified Parkinson's Disease Rating Scale.

*The OR for the association between MPS and treated hypertension was 1.24 (95% CI, 0.99-1.56) ($P = .06$). The OR for the association between MPS and treated diabetes mellitus was 1.21 (95% CI, 0.91-1.62) ($P = .19$).

†For each disease, the second set of data represents the results of analyses in which MPS were defined as present when any UPDRS rating was 1 or higher ($n = 641$ or 28.0% of participants) and absent when all UPDRS ratings were 0.

‡Adjusted for age in years, sex, years of education, CES-D score, and arthritis.

Table 4. Associations Between Number of Vascular Diseases and Mild Parkinsonian Signs (MPS) Subscores in Adjusted Logistic Regression Analyses*

	Changes in Axial Function		Rigidity		Tremor	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
No. of vascular diseases						
All participants	1.19 (1.02-1.38)	.03	1.35 (1.18-1.53)	<.001	1.14 (0.94-1.39)	.19
Excluding participants with stroke	1.13 (0.93-1.37)	.21	1.24 (1.05-1.46)	.01	1.18 (0.93-1.50)	.16
No. of nonvascular diseases						
	0.97 (0.76-1.22)	.77	0.95 (0.77-1.17)	.61	0.67 (0.46-0.97)	.03

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; OR, odds ratio.

*Adjusted for age in years, sex, years of education, CES-D score, and arthritis.

thalamus, and the striatum). One possibility is that these accumulated vascular pathological changes take the form of strokes (ie, stroke as a mediator of the association between vascular risk factors and MPS). However, our finding in some analyses that removal of participants with stroke did not appreciably change the magnitude of the associations between hypertension, diabetes, and MPS (Table 3) suggests that accumulated vascular pathological changes might not be in the form of clinically apparent strokes.

It is well-known that “vascular pseudoparkinsonism” can occur in the setting of basal ganglia infarcts or deep white matter ischemic lesions.^{6,7,20-22} These patients typically have moderate to severe gait disturbance as well as rigidity and bradykinesia in the absence of rest tremor.^{6,7,20} Yet there have been few (2) studies examining vascular risk factors or vascular disease and their association with MPS in normal elderly cohorts with only mild parkinsonism. In the first study,⁸ which included elderly subjects whose Mini-Mental State Examination score was lower than the expected age- and education-specific value, participants with rigidity and gait disturbance were compared with participants without these characteristics; participants with rigidity and gait disturbance were more likely to have hypertension and low high-density lipoprotein cholesterol levels, although the 2 groups did not differ with regard to the proportions with diabetes mellitus, obesity, smoking cigarettes, or high low-density lipoprotein cholesterol levels. In the second study,⁹ the relation between diabetes mellitus and parkinsonian-like signs was assessed prospectively and longitudinally in 822 older Catholic clergymen and women without PD or dementia; the investigators found that diabetes was associated with progression of rigidity and gait disturbance. Overall, these 2 studies suggest that some vascular diseases are associated with MPS and the progression of MPS.

Although we found an association between several vascular diseases and MPS, we did not find a consistent association between MPS and hypertension (ie, the association between MPS and hypertension was only apparent on a secondary analysis). One possible explanation is the high prevalence of this condition in our sample. If the sample is too homogeneous in terms of a history of hypertension, finding a relation between hypertension and MPS may not be possible, even if it exists. In addition, our definition of hypertension did not take into account its duration and severity. Persons with more severe and longer-duration hypertension are more likely to have heart disease, peripheral vascular disease, and stroke. The error in the ascertainment of hypertension and its high prevalence in our sample likely biased our estimates of the association between hypertension and MPS toward the finding of no association. Better measurements of hypertension severity, such as left ventricular hypertrophy ascertained by electrocardiogram or echocardiogram, may be needed to assess this association.

Our study has several limitations. We ascertained vascular disease by self-report and lacked subclinical measurement of disease such as glycosylated hemoglobin measurement for diabetes, electrocardiogram or echocardiography for heart disease, brain imaging for

stroke, and vascular studies for peripheral vascular disease. This is likely to result in an underestimation of the true prevalence of these conditions and, assuming nondifferential misclassification by MPS, resulted in underestimation of the associations that we report. Second, our analyses were cross-sectional, and this limits the inferences that can be made about the causal nature of the association of history of vascular disease and MPS. A prospective study, which is under way, will examine this issue. We also plan a study using brain magnetic resonance imaging to determine whether indeed MPS are more common in individuals with vs those without evidence on imaging of vascular pathological changes in the brain. Third, our modified UPDRS did not include the assessment of appendicular (limb) bradykinesia so it is possible that we may have underestimated the correlates of MPS. Fourth, it can be difficult in elderly persons and persons with dementia to distinguish paratonia from true rigidity. Therefore, in our analyses, we excluded all participants with dementia. For some analyses, we also excluded participants with reported stroke because stroke can result in spasticity, which on examination, can be difficult to distinguish from increased tone in the setting of rigidity. Despite these limitations, the study had several strengths, including the use of a community-based sample, the size of the sample (>2000 elderly participants), and the adjustment for potential demographic and medical confounders.

In summary, the presence of MPS, and rigidity in particular, in elderly individuals might reflect, in part, the accumulation of vascular pathological changes in the basal ganglia or white matter regions caused by preventable vascular disease. Prospective studies as well as imaging and pathological studies are needed to further explore this finding.

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