Motor impairment in PD

Relationship to incident dementia and age

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Article abstract—*Objective:* To analyze the relationship of specific motor impairment in idiopathic PD to incident dementia. *Background:* The total Unified PD Rating Scale (UPDRS) motor score at baseline has been associated with an increased risk of developing dementia in PD. *Methods:* A cohort of 214 nondemented community-dwelling patients with PD was followed annually with neurologic and neuropsychological evaluations. The association of baseline motor impairment with incident dementia was analyzed using Cox proportional hazards models. Facial expression, tremor, rigidity, and bradykinesia were analyzed as part of subscore A (indicative of dopaminergic deficiency); speech and axial impairment were analyzed as part of subscore B (indicative of predominantly nondopaminergic deficiency). The correlation between the six motor domains and age was also analyzed. *Results:* Of 173 patients followed for at least 1 year, 50 became demented according to the Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition (DSM III-R) criteria (mean follow-up, 3.6 ± 2.2 years). When both subscores A and B were entered into the Cox model, subscore B was associated with incident dementia (relative risk = 1.19; 95% CI, 1.09 to 1.30; $p = 0.0001$), in addition to gender, age, and education, whereas subscore A was not (relative risk = 1.03; 95% CI, 0.99 to 1.07; $p = 0.19$). Of the six motor domains, speech and bradykinesia were associated with incident dementia ($p < 0.05$), and axial impairment approached significance ($p = 0.06$). Only axial impairment was correlated with age (correlation coefficient = 0.32; $p < 0.001$). *Conclusion:* The findings suggest that motor impairment mediated predominantly by nondopaminergic systems is associated with incident dementia in PD. Axial impairment may be the result of a combined effect of the disease and the aging process.

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The relationship between specific motor signs and cognitive abilities in idiopathic PD has been extensively evaluated in cross-sectional studies including both demented and nondemented patients.[1-7] In longitudinal studies of patients with PD, age, severity of extrapyramidal signs, depressive symptoms, and specific neuropsychological impairment at baseline have been independently associated with an increased risk of developing dementia.[8-11] However, the association of specific motor impairment to incident dementia in PD has rarely been explored.[12,13]

Some of the motor impairment in PD has been attributed to nondopaminergic mechanisms, as judged by specific signs being relatively refractory to L-dopa therapy, especially in the middle and late stages of the disease.[14] In a cross-sectional study,[15] the motor disability of patients with variable duration of PD was assessed when the L-dopa effect was considered to be maximal and after withdrawal of the medication. The effect of L-dopa on akinesia, rigidity, and tremor remained stable over the different lengths of disease duration, whereas percent improvement on L-dopa decreased for gait disorder, postural instability, and dysarthria. In other studies in which patients with PD on L-dopa were followed for 10 or more years, abnormalities in gait, posture, balance, and speech clearly worsened, whereas other parkinsonian features improved, remained unchanged, or rarely worsened.[16,17] Thus, tremor, rigidity, and bradykinesia may be viewed as representing more purely dopaminergic manifestations of PD. In contrast, speech, posture, balance, and gait disorders may be mediated by other neurotransmitter systems in addition to dopamine.

The biologic basis of dementia in PD is controversial. The correlation between motor and cognitive impairment has been seen as evidence in favor of the contribution of subcortical pathology to the development of dementia in patients with PD.[2,3,5] The analysis of the relationship of specific motor impairment to incident dementia may help clarify the relative contribution of dopaminergic and nondopaminergic neural systems to the development of dementia in PD. We studied the association of Unified PD Rating Scale (UPDRS) motor subscores at baseline and incident dementia in a community-dwelling cohort of nondemented patients with PD followed longitudinally.

Methods. *Subjects.* A cohort of 214 nondemented patients with idiopathic PD from the Washington Heights

Table 1 *Unified PD Rating Scale subscores*

Total UPDRS*	UPDRS domains and subscores		
Facial expression (4 points)	Facial expression (4 points)		
Tremor at rest (20 points)	Tremor (28 points)		
Action or postural tremor (8 points)			
Rigidity (20 points)	Rigidity (20 points)	Subscore A (80 points)	
Hand movements (8 points)			
RAM of hands (8 points)			
Leg agility (8 points)	Bradykinesia (28 points)		
Body bradykinesia and hypokinesia (4 points)			
Speech (4 points)	Speech (4 points)		
Arising from a chair (4 points)			Subscore B (20 points)
Posture (4 points)	Axial impairment (16 points)		
Postural stability (4 points)			
Gait (4 points)			

* Each single test of the UPDRS is rated from 0 (normal) to 4 (severe impairment); tremor at rest is evaluated in the four limbs and face, rigidity is evaluated in the four limbs and neck, and other tests are evaluated bilaterally either in the upper or lower limbs.

RAM = rapid alternating movements; UPDRS = Unified PD Rating Scale.

community in northern Manhattan, New York was followed annually with neurologic and neuropsychological evaluations. The ascertainment procedure and inclusion and exclusion criteria for the cohort have been described previously.[18] Thirty patients were not included in the analysis of the relationship of motor impairment at baseline to incident dementia because they had only one visit. Four patients were excluded because of signs or symptoms of stroke, and data were incomplete for seven patients. Duration of PD was defined as the time period between the first symptom of PD and the baseline evaluation. The neuropsychological battery included tests of verbal and nonverbal memory, orientation, visuospatial ability, language, and verbal and nonverbal abstract reasoning; test scores were evaluated using a fixed paradigm.[19] The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, revised 3rd edition (DSM III-R).[20]

Data analysis. The analysis of the relationship of motor impairment to incident dementia in PD was performed using Cox proportional hazards models. The UPDRS motor examination (part III)[21] was subdivided clinically into six domains: speech, facial expression, tremor, rigidity, bradykinesia, and axial impairment (table 1). First, facial expression, tremor, rigidity, and bradykinesia were analyzed as part of subscore A, and speech and axial impairment were analyzed as part of subscore B. Second, in order to further define the motor impairment associated with incident dementia in PD, the six domains of the UPDRS were entered into the Cox model using a forward stepwise approach for the selection of predictor variables (entry crite-

rion: $p < 0.05$; removal criterion: $p > 0.1$). Duration of follow-up until the diagnosis of dementia or until the last visit for those patients that did not become demented was used as the timing variable in the Cox model. The analyses controlled for age, gender, education, duration of PD, use of dopaminergic (including L-dopa and dopaminergic agonists) and anticholinergic medications.

Because age may confound the relationship between motor and cognitive impairment in PD, the correlation between the six domains of the UPDRS and age was also studied using bivariate and partial correlation analysis. Student's t-tests and χ^2 tests were used for the comparison of continuous and categorical variables at baseline.

Results. Of 173 patients, 50 became demented during a mean follow-up period of 3.6 ± 2.2 years. Baseline characteristics of the cohort are summarized in table 2. Patients that subsequently became demented were older, less educated, and had more severe motor signs at baseline than those who did not become demented. No significant differences were seen in gender, ethnicity, duration of PD, language in which the neuropsychological tests were administered (English or Spanish), total Hamilton Depression Rating Scale[22] score, use of dopaminergic and anticholinergic medications, or L-dopa dosage. The patients that were excluded from the analysis due to missing data (n = 7) were not significantly different from the other patients in terms of gender, age, ethnicity, education, duration of PD, or language in which the neuropsychological tests were administered.

The total UPDRS motor score (range, 0 to 100) was associated with incident dementia in the Cox model (relative risk [RR] = 1.06; 95% CI, 1.04 to 1.09; $p < 0.0001$), independent of demographic and medication variables. This risk ratio means that a one-point difference in total UPDRS motor scores between two subjects with similar demographic profiles would be associated with a 6% increase in risk of dementia over the 3.6 year follow-up period. Both subscore A (RR = 1.07; 95% CI, 1.03 to 1.10; $p = 0.0003$) and subscore B (RR = 1.23; 95% CI, 1.14 to 1.32; $p < 0.0001$) were associated with incident dementia when entered separately into the model. When both were entered into the model, subscore B but not subscore A was significantly associated with incident dementia. Male gender, age at baseline, and education were also significantly associated with incident dementia in this model (table 3). The analysis was repeated using L-dopa dosage rather than use of dopaminergic medications as a covariate. Nineteen additional cases were lost due to missing information about L-dopa dosage; subscore B (RR = 1.17; 95% CI, 1.06 to 1.29; $p = 0.002$) was still associated with incident dementia but subscore A (RR = 1.04; 95% CI, 1.00 to 1.08; $p = 0.07$) was not. In a separate analysis including the six domains of the UPDRS, speech and axial impairment (subscore B) as well as bradykinesia (subscore A) were retained in the final model, although axial impairment approached significance (table 4).

Among the six UPDRS motor domains, axial impairment (Spearman's rank correlation coefficient = 0.29; $p < 0.001$) (figure) and speech (Spearman's rank correlation coefficient = -0.15; $p = 0.03$) were correlated with age. The motor domains, with the exception of tremor and rigidity, were correlated with duration of PD ($p < 0.001$). When the analysis of the correlation between age and the

Table 2 *Baseline demographic and clinical characteristics of PD patients who did and did not become demented*

Variable	Incident dementia (n = 50)	No incident dementia (n = 123)	Total (n = 173)
Age, y	74.3 (8.2)	69.4 (10.8)*	70.8 (10.3)
Education, y	9.5 (4.7)	11.8 (4.7)*	11.1 (4.8)
Gender, % male	56.0	43.1	46.8
Ethnicity, % white and non-Hispanic	56.0	53.7	54.3
Language, % English	51.0	64.8	60.8
Duration of PD, y	7.5 (5.9)	5.8 (7.3)	6.3 (7.0)
Total UPDRS score	31.4 (13.1)	22.0 (11.4)*	24.8 (12.6)
Total HDRS score†	7.0 (5.6)	5.6 (5.0)	6.0 (5.2)
Use of dopaminergic medications, %‡	76.0	74.8	75.1
Use of anticholinergic medications, %	18.0	15.4	16.2
L-dopa dosage, mg/day§	326.7 (325.3)	333.3 (335.4)	331.5 (331.6)

Values are expressed as mean (SD).

* $p < 0.05$.
† Total n = 147.
‡ Includes L-dopa and dopaminergic agonists.
§ Total n = 154.

HDRS = Hamilton Depression Rating Scale; UPDRS = Unified PD Rating scale.

motor domains was repeated controlling for duration of PD and L-dopa dosage, the positive correlation between axial impairment and age was still significant (correlation coefficient = 0.32; $p < 0.001$), but the negative correlation between speech and age was not significant anymore (correlation coefficient = −0.13; $p = 0.09$). Each of the four tests of the UPDRS that were included in the axial impairment domain (rising from a chair, posture, gait, and postural stability) were also significantly correlated with age.

Discussion. Our findings suggest that PD motor impairment mediated predominantly by nondopaminergic systems is associated with incident dementia. When the UPDRS total motor score was divided in two subscores according to relative responsiveness to dopaminergic therapy, motor impairment partially responsive or nonresponsive to L-dopa (subscore B) predicted the development of dementia in PD, whereas in the same model, motor impairment responsive to L-dopa throughout the course of the disease (subscore A) did not. Among six domains of extrapyramidal motor impairment in PD, speech and bradykinesia predicted the development of incident dementia, and axial impairment approached significance in the Cox model.

Among the motor domains believed to respond to L-dopa throughout the course of the disease, bradykinesia was the only one to be significantly associated with incident dementia. Indeed, bradykinesia has been associated with cognitive impairment in PD in many cross-sectional[1-5] and longitudinal[12,13] studies. Other evidence, however, suggests a stronger relationship between non–L-dopa-responsive motor manifestations and cognitive impairment in PD. In one study,[23] none of the neuropsychological test scores was correlated with the L-dopa-responsive motor score (the difference between the motor score after withdrawal of L-dopa and the motor score on L-dopa

Table 3 *Risk ratios for incident dementia derived from a Cox proportional hazards model including subscores A and B*

Variable	Risk ratio	95% CI	p Value
Male gender	2.57	1.43–4.61	0.002
Age at baseline	1.09	1.05–1.13	<0.0001
Education	0.93	0.88–0.99	0.02
Duration of PD	0.97	0.94–1.01	0.10
Use of DA	0.96	0.47–1.94	0.91
Use of anticholinergics	1.62	0.73–3.60	0.24
UPDRS subscore A	1.03	0.99–1.07	0.19
UPDRS subscore B	1.19	1.09–1.30	0.0001

DA = dopaminergic agent; UPDRS = Unified PD Rating Scale.

Table 4 *Risk ratios for incident dementia derived from a Cox proportional hazards model including UPDRS motor domains*

Variable	Risk ratio	95% CI	p Value
Male gender	2.04	1.07–3.90	0.03
Age at baseline	1.11	1.06–1.15	<0.0001
Education	0.95	0.89–1.01	0.09
Duration of PD	0.97	0.93–1.00	0.04
Use of DA	0.79	0.39–1.62	0.52
Use of anticholinergics	1.46	0.66–3.24	0.35
Speech	1.67	1.13–2.49	0.01
Bradykinesia	1.09	1.01–1.18	0.02
Axial impairment	1.11	0.99–1.24	0.06

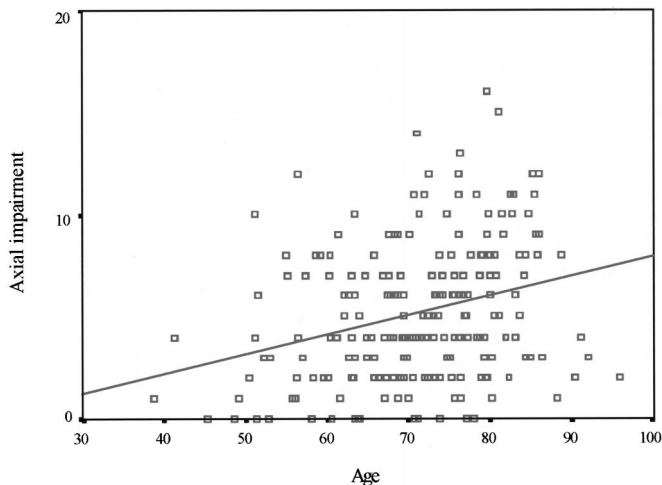DA = dopaminergic agent; UPDRS = Unified PD Rating Scale.

Figure. Scatterplot and fit line of axial impairment versus age.

treatment), but all were highly correlated with the motor score on L-dopa treatment (motor impairment not alleviated by L-dopa and presumed to be the result of nondopaminergic lesions). Moreover, cognitive impairment was poorly correlated with akinesia and rigidity, strongly correlated with gait disorder and dysarthria, and not correlated with tremor at all. In an analysis of the DATATOP cohort,[24] a postural instability and gait disorder subtype of PD was associated with a more rapid disease progression and greater subjective intellectual impairment as compared with a tremor-dominant subtype of PD.

Among the six motor domains, only axial impairment was significantly correlated with age in our study. The relationship between gait and posture impairment and age has been demonstrated in other studies,[4,25] and patients with young-onset PD are less likely to complain of difficulty walking as an early symptom compared with patients with late-onset PD.[26] Thus, age may act as a confounder and at least partly explain the strong correlation of gait and postural disturbances with cognitive impairment in univariate analyses. In one previous analysis,[13] rigidity, posture, gait, "bradykinesia of hands," "upper extremity swing," and "hoarseness and weakness of speech" were significantly associated with dementia in the univariate analysis. However, only bradykinesia and speech impairment were significant predictors of dementia in a logistic regression model controlling for age. In our analysis, the axial impairment contribution to the Cox model controlling for age and other covariates approached significance. Extrapyramidal manifestations resembling parkinsonian features have long been recognized in normal aging, including "an attitude of general flexion," rigidity, poverty of movement, bradykinesia, and gait disorders.[27] However, the unique correlation between axial impairment and age in the setting of PD suggests a combined effect of the disease and the aging process.

The strengths of this study include the large co-

hort of community-dwelling patients with PD followed for a relatively long period with neurologic and neuropsychological evaluations, and its distinct methodologic approach. Nevertheless, the implications of our findings for the contribution of dopaminergic and nondopaminergic mechanisms to the development of dementia in PD rest upon the assumption that nondopaminergic lesions play a predominant role in speech and axial impairment in the middle and late stages of PD, and underlie the declining L-dopa responsiveness over the course of the disease.[14,16] Although in a recent study bradykinesia was the clinical sign of PD with the highest correlation with the degree of nigrostriatal dopaminergic deficit measured by fluorodopa PET,[28] pathologic, pharmacologic, and experimental animal data suggest that dopamine is also related to rigidity and rest tremor.[29,30] Evidence from human parkinsonism due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) also indicates that dopamine deficiency may underlie the three cardinal signs of PD.[31] Other weaknesses of this study include the lack of autopsy data allowing for clinical-pathologic correlation, and the fact that our cohort consisted of patients with a mean disease duration at baseline of 6.3 years. Therefore, our results may not be applicable to patients with early PD.

The role of nondopaminergic structures in the cognitive manifestations of PD is supported by pathologic studies demonstrating greater involvement of the basal forebrain[32,33] and locus ceruleus[34,35] in patients with PD and dementia compared with those with PD without dementia. Loss of neurons in the nucleus basalis of Meynert has been observed in PD independently of Alzheimer-type cortical pathology.[36,37] Nondopaminergic structures have also been implicated in PD motor manifestations. Cell loss in the pedunculopontine nucleus containing cholinergic neurons (Ch5 cholinergic cell group[38]) has been shown in PD and, to a greater extent, in progressive supranuclear palsy.[39-41] That the pedunculopontine nucleus may play a role in the parkinsonian gait disorder is supported by animal experimental studies showing its relationship to a mesencephalic locomotor region,[42,43] and by its connections to the thalamus, basal ganglia, subthalamic nucleus, and substantia nigra, as well as to other sites in the brainstem and spinal cord.[44,45] The locus ceruleus (noradrenergic), in turn, has been implicated in the motor phenomenon of freezing[46,47] and, through a facilitatory influence on nigrostriatal and mesolimbic dopaminergic pathways, in locomotion behavior based on animal studies.[48,49]

We believe that patients with PD with a greater risk of developing dementia may exhibit a more widespread neurotransmitter deficiency resulting from subcortical pathology prior to the onset of dementia. The brainstem nondopaminergic structures (locus ceruleus and pedunculopontine nucleus) may be involved in both motor impairment (subscore B) and the development of dementia in PD, or degenerate in parallel with the cholinergic system of the

basal forebrain. Moreover, axial motor impairment in PD may be the result of a combined effect of the disease and the aging process in brainstem nondopaminergic structures. To further clarify these issues, clinical-pathologic correlation exploring cognitive function and specific motor manifestations of PD and dopaminergic as well as nondopaminergic anatomic structures is needed.

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Cerebral blood flow and glucose metabolism in mitochondrial disorders

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Article abstract—*Objective:* To investigate cerebral metabolism by 2-[^{18}F]fluorodeoxy-D-glucose (FDG) uptake using PET and cerebrovascular reverse capacity by transcranial Doppler sonography (TCD) in different mitochondrial diseases (mitochondrial myopathy; mitochondrial encephalopathy, lactacidosis, and stroke-like episodes [MELAS]; and chronic external ophthalmoplegia). *Background:* Previous studies on individual patients with mitochondriopathies revealed abnormal accumulations of mitochondria in endothelium, smooth muscle cells, and pericytes of blood vessels in different parts of the nervous system (cerebrum, cerebellum, sural nerve) and skeletal muscle. On this basis, some investigators suggested a pathogenic role of vascular involvement in the MELAS syndrome and other encephalopathies. *Design/Methods:* The authors investigated neuronal metabolism and cerebrovascular involvement with PET in 5 cases and with TCD with acetazolamide stimulation in 15 cases. The patients were divided into three groups: 1) interictal MELAS (n = 4); 2) progressive external ophthalmoplegia (n = 6); and 3) pure mitochondrial myopathy and neuropathy (n = 5). The results were compared with those from matched normal control subjects. The diagnoses were based on clinical phenotype as well as histopathologic and molecular analysis. *Results:* Cerebral glucose uptake was impaired in all patients, both with and without CNS symptoms, particularly in the occipital and temporal lobes. The vasoreactivity of the small arterioles to acetazolamide did not differ significantly between the patients and healthy control subjects or between the different groups of mitochondrial disorders. *Conclusions:* MELAS does not appear to be a functional disturbance of arterioles leading to an ischemic vascular event. The clinical symptoms in MELAS are not the result of a mitochondrial angiopathy but are the consequences of a mitochondrial cytopathy affecting neurons or glia. There is no correlation between the decreased glucose metabolism and the duration of the disease.

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Mitochondrial diseases are systemic disorders usually affecting multiple organs. Owing to the different minimum energy requirements necessary for the function of different organs, mitochondrial diseases can result in tissue-specific disorders.[1] The susceptibility of the CNS to mitochondrial dysfunction

because of its high dependence on oxidative metabolism has been well recognized.[2] However, the functional involvement of the CNS may be difficult to detect. In certain mitochondrial encephalomyopathies, characteristic changes may be found in the CNS by CT.[3] In some cases, diffuse hypodensity in CT or increased water signal on MRI can be present without clinical CNS symptoms; in turn, MRI or CT signal changes may not yet be detectable when clinical symptoms are already manifested. However, neu-

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G. Levy, M.-X. Tang, L.J. Cote, et al.

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