Mortality From Parkinson Disease

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Background: Levodopa therapy for Parkinson disease (PD) has improved quality of life, but mortality rates remain high. Although the presence of dementia and severity of extrapyramidal signs (EPSs) influence morbidity in PD, it is not known whether these manifestations contribute to mortality.

Methods: Patients with PD were compared with nondemented and demented elderly subjects. Each underwent annual neurological and neuropsychological examinations. Dementia was diagnosed by *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* criteria, and EPSs were rated with the Unified Parkinson's Disease Rating Scale. Survival rates were compared using Kaplan-Meier analysis and Cox proportional hazards models.

Results: The risk of mortality, when compared with nondemented elderly subjects, was highest among those with both PD and dementia (rate ratio, 4.9; 95% confidence interval, 3.4-7.1), but also was elevated in patients with PD only (rate ratio, 2.7; 95% confidence interval, 1.7-4.4). Dementia in the absence of PD also was associated with an increased risk of mortality (rate ratio, 1.6; 95% confidence interval, 1.1-2.3). A high baseline total EPS score was associated with significantly earlier mortality.

Conclusions: Compared with nondemented elderly people in the same community, patients with PD have a 2- to 5-fold increased risk of mortality. The risk is strongly related to the presence of severe EPSs, especially bradykinesia. Despite the introduction of levodopa and other advances in the treatment of PD, these factors greatly increase mortality.

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THE DEVELOPMENT of levodopa therapy for Parkinson disease (PD) has improved the quality of life for most patients.[1] Despite this, mortality rates among those with PD remain higher than expected for age.[2-5] Although the presence of dementia or severity of extrapyramidal signs (EPSs) contribute to morbidity and disability in PD, it is uncertain whether these factors contribute to mortality. In this study, we (1) compare survival rates in patients who have PD with persons of similar age from the same community in northern Manhattan, New York and (2) assess the contribution of several variables, including EPSs and dementia, to mortality in PD.

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RESULTS

Among 288 patients with PD, 134 (46.5%) were demented and 154 (53.5%) were not. In the comparison group, 436 (25.8%) were demented and 1254 (74.2%) were not (**Table 1**). Compared with nondemented elderly subjects, risk of mortality was highest for those with both PD and dementia (RR, 4.9; 95% confidence interval [CI], 3.4-7.1), but was also elevated in those with PD only (RR, 2.7; 95% CI, 1.7-4.4), after adjusting for baseline age, years of education, sex, ethnicity, and smoking status (Table 1 and **Figure**). Demented subjects in the comparison group also had an increased risk of mortality (RR, 1.6; 95% CI, 1.1-2.3) after adjusting for baseline age, years of education, sex, ethnicity, and smoking status (Table 1 and Figure). The risk of mortality in all 288 patients with PD was 4.1 (95% CI, 3.0-5.6) compared with nondemented elderly subjects, after adjusting for baseline age, education, sex, ethnicity, and smoking status.

We next analyzed data in the 288 patients with PD. Disease duration and proportion taking levodopa are given in **Table 2**. Total baseline EPS score was examined as a categorical and as a continuous covariate in a Cox model (**Table 3**). In both instances, EPS score was associated with significantly earlier mortality, but

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PATIENTS AND METHODS

PATIENTS WITH IDIOPATHIC PD

A community-based registry of patients with idiopathic PD has been in existence in Manhatten since 1988. A survey of Medicare recipients indicated that the registry was complete for the ascertainment of persons with PD living in the 3 contiguous ZIP codes within the project target area in northern Manhattan.[6] All diagnoses were confirmed by 1 of 4 neurologists (E.D.L., K.M., L.C., or R.M.) based on a standardized neurological evaluation. Idiopathic PD, defined by clinical and research criteria,[6-9] did not include drug-induced parkinsonism or parkinsonian plus syndromes.

All patients with PD underwent a standardized neuropsychological battery[10] and were considered demented if they met established criteria[11] and if functional difficulties could be attributed to cognitive rather than physical disability.[12]

A baseline total EPS score was calculated by summing the scores of the individual items in the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) (maximum score=100).[13] Subjects with PD were divided into 2 groups: those below and including the median EPS score and those above the median EPS score. Baseline scores for individual motor items, including rest tremor, rigidity, bradykinesia, and postural or gait abnormalities, were calculated from the motor portion of the UPDRS (eg, a baseline rigidity score was calculated by summing the scores on the 5 rigidity items in the UPDRS. A baseline postural or gait abnormalities score was calculated by summing the scores on the 4 items in the UPDRS dealing with arising from a seated position, standing, walking, and balance).

DEMENTED AND NONDEMENTED ELDERLY SUBJECTS

The source population for the comparison group was the elderly population of Washington Heights–Inwood, New York. The Health Care Financing Association provided a random sample of names and addresses of all Medicare recipients in 3 contiguous ZIP codes in northern Manhattan. Potential subjects were sent a letter from the Health Care Financing Association explaining that they had been selected as potential participants in a study of aging. The 72% who agreed to participate underwent a 90-minute in-person interview conducted in English or Spanish, depending on the subject's preference. The interview was conducted by trained interviewers. All participants who performed below a standard cutoff score for a mental status screen also underwent standardized neurological and neuropsychological testing, as did a 25% sample of those performing within the normal range. Participants were considered demented if they met the same research criteria previously described.[11,12]

ASSESSMENTS

Patients with idiopathic PD and demented and nondemented elderly subjects were evaluated at baseline and at yearly intervals. Extrapyramidal signs were rated by 4 raters (E.D.L., K.M., L.C., and R.M.) using the motor portion of the UPDRS,[13] and these ratings have been shown to be reliable.[14]

Information on age, sex, ethnicity, medications, years of education, and medical history was collected. Information on whether a subject was taking levodopa was collected at baseline and annually. Data on levodopa dose was not collected at baseline, but was collected between years 4 and 5 of the study. The calculation of mean daily dose of levodopa included only those who were taking levodopa during that period. Smoking status was coded as "yes" or "no" for the question, "Did you ever smoke cigarettes, cigars, or a pipe?" For ethnic group classification, we used the format suggested by the 1990 US Census Bureau.[15] Assessment of performance of activities of daily living was rated by the physician using the Schwab and England Activities of Daily Living scale.[16] Death information was obtained from the family, hospital records, death certificates, autopsy reports, and death records of the National Death Index.

DATA ANALYSIS

Those with stroke (n=33) were excluded from these analyses. There were no other exclusions. The χ^2 test, 2-tailed Student t test or its standard normal approximation (z), analysis of variance, and correlation coefficient (r) were used to determine statistical significance. Survival was examined using Kaplan-Meier plots.[17] Cox proportional hazards analysis[18] was used to estimate rate ratios (RRs) for the main outcome measure (death) in those with PD and/or dementia vs nondemented elderly subjects, adjusting for categorical variables (sex, ethnicity, and smoking status) and continuous variables (age at baseline and years of education) in a forward stepwise model. Cox proportional hazards analysis[18] also was used to estimate risk of mortality in those with PD (demented and nondemented), adjusting for categorical variables (sex, ethnicity, dementia, total baseline EPS score [high vs low], and use of levodopa or dopamine agonist at any time) and continuous variables (age at baseline, years of education, disease duration, and total baseline EPS score) in a forward stepwise model. The starting date for the survival analysis was the date of enrollment in the study rather than date of diagnosis of PD, so the time variable used in the Cox model was age at death rather than duration of disease. Age is a more appropriate variable, because subjects, especially if demented, may not recall precisely the date of onset of symptoms, especially if those symptoms are subtle or difficult to label or identify. Duration of disease was treated as a covariate.

sex, ethnicity, years of education, smoking status, disease duration, or use of levodopa or dopamine agonists at any time were not. When high total baseline EPS score was included along with dementia in the Cox model, dementia was not a significant independent risk factor for mortality (Table 3). There was no correlation between the total baseline EPS score and levodopa dose ($r=-0.16$; $P=.20$). Although demented subjects with PD were less likely than nondemented subjects with PD to take levodopa at any time (65.4% vs 74.5%) and had a lower mean daily levodopa dose (427.8 vs 567.1 mg), neither comparison was significant.

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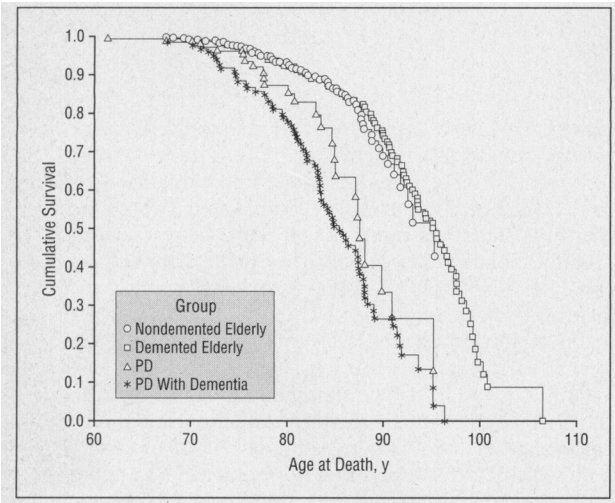
Table 1. Demographic and Mortality Data in Subjects*

Characteristic	PD With Dementia	PD Only	Demented Elderly	Nondemented Elderly	P
No. of subjects	134	154	436	1254	...
Mean baseline age, y	78.3	70.4	81.3	73.3	<.001 (ANOVA)
Male, %	53.0	48.1	20.2	32.6	<.001 (×2)
Ethnicity, %					<.001 (ANOVA)
African American	14.2	11.7	34.2	14.8	...
Caucasian	47.8	50.0	9.2	25.4	...
Hispanic	36.5	36.4	54.3	59.3	...
Other	1.5	1.9	2.3	0.5	...
Mean follow-up, y†	2.1 [3.1]	2.5 [3.5]	1.8 [2.6]	0.8 [2.4]	<.001 (ANOVA)
History of smoking, %	50	42.7	34.8	50.7	<.001 (×2)
Education, mean No. of grades	9.2	11.2	6.4	9.1	<.001 (ANOVA)
Mean total baseline EPS score	38.7	24.5	NA	NA	<.001 (z)
Mean baseline activities of daily living score	53.8	79.2	63.1	91.1	<.001 (ANOVA)
No. (%) of deaths	74 (55.2%)	24 (15.6%)	110 (25.7%)	76 (6.1%)	<.001 (×2)
Mortality RR (95% confidence interval), P‡	4.9 (3.4-7.1), <.001	2.7 (1.7-4.4), .001	1.6 (1.1-2.3), <.02	1.0 (reference group)	...

*PD indicates Parkinson disease; ANOVA, analysis of variance; EPS, extrapyramidal sign; NA, not available; and RR, rate ratio.

†Values in brackets represent subjects who were followed up after baseline evaluation and excludes subjects who were not followed up after the initial baseline evaluation. The number of subjects followed up after the baseline evaluation was 92 (PD with dementia), 107 (PD only), 300 (dementia only), and 385 (nondemented elderly). Range of follow-up was 0 to 7 years.

‡Adjusting for baseline age, years of education, gender, ethnicity, and smoking status in a Cox model.



Kaplan-Meier survival curve comparing survival in 4 groups. After adjusting for age, education, sex, ethnicity, and smoking status in a Cox model, the demented elderly had a modest increased risk of mortality compared with the nondemented elderly (mortality rate ratio, 1.6). PD indicates Parkinson disease.

Table 2. Characteristics of 288 Patients With Parkinson Disease*

Characteristic	Value
Disease duration at baseline, y	
Mean (range)	6.3 (<1-46.8)
Median (range)	4.5 (<1-46.8)
Median (range) baseline score	
Total EPSs	28 (2-84)
Rigidity	7.2 (0-20)
Rest tremor	2.5 (0-15)
Bradykinesia	10.4 (0-28)
Postural or gait disorder	6.6 (0-16)
No. (%) taking levodopa at any time	196 (68.1)
No. (%) taking a dopamine agonist at any time	69 (36.7)

*EPSs indicates extrapyramidal signs.

Table 3. Predictors of Mortality in 288 Patients With Parkinson Disease*

Variable	Mortality Rate Ratio	95% Confidence Interval	P
High total baseline EPS score†	2.0	1.2-3.4	<.007
Total baseline EPS score‡	1.02	1.004-1.03	<.009
Dementia at any time§	1.3	0.8-2.3	.30

*EPS indicates extrapyramidal sign.

†EPS score as a categorical variable. A high EPS score is a score above the median EPS score (28).

‡EPS score as a continuous variable (values ranging from 0-100).

§When high EPS score was included in this Cox model, dementia, gender, ethnicity, years of education, smoking status, disease duration, use of levodopa, or use of dopamine agonists at any time were not associated with increased risk of mortality.

We further analyzed the contributions of dementia and total baseline EPS score on mortality by stratifying those with PD into 4 groups based on dementia (present or absent) and total baseline EPS score (high or low). Those with low baseline EPS score and no dementia were used as a reference group (**Table 4**). High total baseline EPS score was associated with increased risk of mortality (RR, 3.4; 95% CI, 1.5-7.6), regardless of the presence or absence of dementia (Table 4). Among those with high total baseline EPS score, there was no difference in the risk of mortality between those with PD and dementia vs those with PD only (RR, 1.0). Dementia contributed to increased mortality only in those with low total baseline EPS scores (RR, 2.3; 95% CI, 1.1-4.9).

We subanalyzed the different EPSs in those with PD for their effect on mortality. Signs included rest tremor, rigidity, bradykinesia, and postural or gait abnormalities. Subjects were divided into those with severe vs mild baseline signs based on the median scores (Table 2). In a Cox model, only severe bradykinesia (RR, 1.8; 95% CI, 1.2-2.7; P=.01) was associated with increased risk of mor-

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Table 4. EPS Score and/or Dementia as Predictors of Mortality in 283 Patients With Parkinson Disease*

EPSs	PD With Dementia (n=129)	PD Only (n=154)
Total baseline score		
High (n=136)	n = 84 RR = 3.4 (95% CI = 1.5-7.6)	n = 52 RR = 3.4 (95% CI = 1.5-7.6)
Low (n=147)	n = 45 RR = 2.3 (95% CI = 1.1-4.9)	n=102 RR = 1.0 (reference group)

*EPSs indicates extrapyramidal signs; PD, Parkinson disease; RR, mortality rate ratio after adjusting for baseline age, years of education, sex, ethnicity, and smoking status in a Cox model; and CI, confidence interval.

Table 5. Causes of Death*

Cause of Death	PD With Dementia	PD Only	Demented Elderly	Nondemented Elderly	χ^2 (*P*)
Pneumonia	9	0	4	0	19.5 (.001)
Myocardial infarction	3	1	2	3	1.8 (.62)
Nonischemic cardiovascular	8	4	1	2	0.42 (.94)
Cerebrovascular	3	0	0	2	25.98 (.001)
Neoplasm	2	0	7	5	10.21 (.02)
Other diseases	13	8	58	5	. . .
Cardiopulmonary	13	3	3	44	4.88 (.18)
Unknown	23	8	35	15	. . .
Total	74	24	110	76	. . .

*PD indicates Parkinson disease.

tality. Severe tremor, rigidity, or gait abnormality did not correlate with increased risk of mortality.

Cause of death was known for most subjects, and pneumonia was more common among those with PD (**Table 5**).

COMMENT

The presence of dementia and the severity of EPSs affect the morbidity and treatment of PD. However, the contribution of each of these factors to the increased mortality in PD is unclear. One case control study suggested that several measures of motor function and impaired performance on a 10-item cognitive screen were predictors of mortality in subjects with PD.[4] We report a modest increased risk of mortality in those with dementia only compared with nondemented elderly people, a greater increased risk of mortality in those with PD only compared with nondemented elderly people, and a marked increased risk of mortality in those with both PD and dementia. The EPS score, perhaps even more than dementia, was the single most important indicator of increased mortality in PD. First, among those with PD (with or without dementia), EPS score, as either a categorical or a continuous variable, was associated with significantly earlier mortality, even after controlling for numerous other variables in a Cox model. When high total baseline EPS score was included along with dementia in the Cox model, dementia was not a significant independent risk factor for mortality. Second, high total baseline EPS score was associated with increased risk of mortality, regardless of the presence or absence of dementia. Dementia contributed to increased mortality only in those with low total baseline EPS scores. Finally, the mean total baseline EPS score, a measure of severity of motor manifestations of PD, was higher among those with both PD and dementia (38.7) than those with PD only (24.5) (z=8.0; $P<.001$). Hence, higher EPS score rather than the presence of dementia may have contributed to greater risk of mortality in the group with both PD and dementia. Bradykinesia was the motor manifestation that most highly correlated with increased mortality.

The increased risk of mortality that we report for those with PD is higher than that reported in other case control studies, with several exceptions.[2,4] The proportion of those with PD and dementia in our study was high (46.5%); this may be related to the ascertainment of cases from the community rather than from a clinic. We report a modest increased risk of mortality in those with dementia only (RR, 1.6; 95% CI, 1.1-2.3). This has been observed in other studies comparing risk of mortality in those who have dementia with healthy controls.[19,20]

This study had limitations. The study was designed to assess prevalence and incidence of PD and dementia associated with PD, and, by design, the length of follow-up was longer for the subjects with PD than for nondemented elderly people. The Cox proportional hazards analysis was used specifically to adjust for this difference in length of follow-up. In addition, we do not know whether the dementia associated with PD is a distinct entity from the dementia observed in our subjects who did not have accompanying PD.

In summary, although the presence of dementia or the severity of EPS affect treatment and morbidity in PD, the contribution of each of these factors to the increased mortality in PD has been unclear. The present study was

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conducted prospectively, and participants underwent a detailed neuropsychological and neurological test battery. Mortality was compared in those with both PD and dementia, PD only, dementia only, and nondemented elderly people, all selected from the same community. We showed in northern Manhattan that risk of mortality is greater in those with PD than in nondemented elderly people. The risk is strongly related to the presence of severe baseline EPSs, especially bradykinesia. Despite the introduction of levodopa and other advances in the treatment of PD, these factors greatly increase mortality.

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REFERENCES

1. Diamond SG, Markham CH. Present mortality in Parkinson's disease: the ratio of observed to expected deaths with a method to calculate expected deaths. *J Neural Transm.* 1976;36:259-269.
2. Ben-Shlomo Y, Marmot MG. Survival and cause of death in a cohort of patients with parkinsonism: possible clues to aetiology? *J Neurol Neurosurg Psychiatry.* 1995;58:293-299.
3. Bennett DA, Beckett LA, Murray AM, et al. Prevalence of and mortality from parkinsonism in a community population of older persons. *N Engl J Med.* 1996; 334:71-76.
4. Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JAO, Mutch WJ. Parkinson's disease in Aberdeen: survival after 3.5 years. *Acta Neurol Scand.* 1990; 81:294-299.
5. Rajput AH, Offord KP, Beard CM, Kurland LT. Epidemiology of parkinsonism: incidence, classification and mortality. *Ann Neurol.* 1984;16:278-282.
6. Mayeux R, Marder K, Cote L, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. *Am J Epidemiol.* 1995;142:820-827.
7. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinicopathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55:181-184.
8. Hughes AJ, Ben-Shlomo Y, Kilford L, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathological study. *Neurology.* 1992;42:1142-1146.
9. Ward CD, Gibb WR. Research diagnostic criteria for Parkinson's disease. *Adv Neurol.* 1990;53:245-249.
10. Stern Y, Andrews H, Pittman J, et al. Diagnosis of dementia in a heterogeneous population: development of a neuropsychological paradigm–based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol.* 1992;49:453-460.
11. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987.
12. Marder K, Tang M-X, Cote L, Stern Y, Mayeux R. The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Arch Neurol.* 1995;52:695-701.
13. Stern MB. The clinical characteristics of Parkinson's disease and parkinsonian syndromes: diagnosis and assessment. In: Stern MB, Hurtig HI, eds. *The Comprehensive Management of Parkinson's Disease.* New York, NY: PMA Publishing Corp; 1978:34-39.
14. Richards M, Marder K, Cote L, Mayeux R. Interrater reliability and factor structure of the Unified Parkinson's Disease Rating Scale Motor Examination. *Mov Disord.* 1994;9:89-91.
15. US Bureau of the Census. Census of Population and Housing, 1990. Washington, DC: US Bureau of the Census; 1991.
16. Schwab JF, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Billingham FH, Donaldson MC, eds. *Third Symposium on Parkinson's Disease.* Edinburgh, Scotland: E & S Livingstone; 1969:152-157.
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
18. Cox DR. Regression models and life-tables. *J R Statist Soc Ser B.* 1972;34: 187-220.
19. Evans DA, Smith LA, Scherr PA, Albert MS, Funkenstein HH, Hebert LE. Risk of death from Alzheimer's disease in a community population of older persons. *Am J Epidemiol.* 1991;134:403-412.
20. Heeren TJ, van Hemert AM, Rooymans HGM. A community-based study of survival in dementia. *Acta Psychiatr Scand.* 1992;85:415-418.

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