Longitudinal study of normal cognition in Parkinson disease

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ABSTRACT

Objective: To report the rates and predictors of progression from normal cognition to either mild cognitive impairment (MCI) or dementia using standardized neuropsychological methods.

Methods: A prospective cohort of patients diagnosed with Parkinson disease (PD) and baseline normal cognition was assessed for cognitive decline, performance, and function for a minimum of 2 years, and up to 6. A panel of movement disorders experts classified patients as having normal cognition, MCI, or dementia, with 55/68 (80.9%) of eligible patients seen at year 6. Kaplan-Meier curves and Cox proportional hazard models were used to examine cognitive decline and its predictors.

Results: We enrolled 141 patients, who averaged 68.8 years of age, 63% men, who had PD on average for 5 years. The cumulative incidence of cognitive impairment was 8.5% at year 1, increasing to 47.4% by year 6. All incident MCI cases had progressed to dementia by year 5. In a multivariate analysis, predictors of future decline were male sex ($p = 0.02$), higher Unified Parkinson's Disease Rating Scale motor score ($p \leq 0.001$), and worse global cognitive score ($p < 0.001$).

Conclusions: Approximately half of patients with PD with normal cognition at baseline develop cognitive impairment within 6 years and all new MCI cases progress to dementia within 5 years. Our results show that the transition from normal cognition to cognitive impairment, including dementia, occurs frequently and quickly. Certain clinical and cognitive variables may be useful in predicting progression to cognitive impairment in PD. ***Neurology*® 2015;85:1276–1282**

GLOSSARY

BNT = Boston Naming Test; **DRS-2** = Dementia Rating Scale–2; **HVLT-R** = Hopkins Verbal Learning Test–Revised; **MCI** = mild cognitive impairment; **NC** = normal cognition; **PD** = Parkinson disease; **PDD** = Parkinson disease dementia; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Nonmotor symptoms are common in Parkinson disease (PD),[1] including mild cognitive impairment (MCI) and dementia (PDD).[2] Up to 80% of patients with PD develop dementia long-term,[3] and 20%–30% of patients with PD without dementia meet criteria for MCI.[4] Both PD-MCI and PDD impact negatively on patient quality of life, cost of care, and caregiver burden.[5,6]

Longitudinal reports on patients with early PD-MCI show that more than 25% will develop dementia within 3 years,[7] and MCI at disease onset increases risk for development of dementia.[8] Another study reported that up to 50% of patients with early PD developed cognitive decline within 5 years,[9] although the sample size was relatively small and lack of cognitive impairment at baseline was defined by Mini-Mental State Examination score only.

Structural MRI, and plasma and CSF biomarkers, are associated with cognitive functioning and predict future cognitive decline in PD.[1] However, many biomarkers are invasive, costly, and done mainly at academic centers conducting research. Demographic and clinical factors such as age,[10] motor subtypes,[11] and early visuospatial, language, and fluency deficits[12,13] have also been shown to predict future cognitive decline. However, to our knowledge, no research has focused on those patients defined as having normal cognition (NC) at baseline, which allows for examination of the course of cognitive decline from its clinical onset.

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Supplemental data at Neurology.org

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We prospectively studied a convenience cohort of patients with idiopathic PD with NC at baseline. The objectives were to observe cognitive outcomes over time to determine baseline demographic, clinical, and cognitive predictors of progression from stringently defined NC to cognitive impairment (PD-MCI or PDD).

METHODS

Participants. Participants in this study were enrolled from 2006 to 2012 in the National Institute of Neurological Disorders and Stroke–funded Morris K. Udall Center for Parkinson's Disease Research at the University of Pennsylvania. A cohort of 141 patients with idiopathic PD and normal cognition at baseline were followed for a minimum of 2 years, and up to 6 years, with baseline and then annual (1 to 4 years of follow-up) or biannual (starting at year 5 of follow-up) neuropsychological testing. PD diagnosis was made based on UK Brain Bank criteria.[14] All participants had a consensus diagnosis of normal cognition at baseline (i.e., those with a baseline MCI or dementia diagnosis were excluded) and PD duration of greater than 1 year; thus none met criteria for dementia with Lewy bodies.[15] As an additional step to exclude for any significant baseline cognitive impairment, participants with a Dementia Rating Scale–2 (DRS-2)[16] total score ≤133 (out of a possible 144 points) at baseline were excluded from analysis regardless of the consensus clinical diagnosis. This number was chosen to be consistent with recent research reporting this as the optimal cutoff on the DRS-2 to identify PDD.[17]

Standard protocol approvals, registrations, and patient consents. Approval from the institutional ethical standards committee on human experimentation was obtained before study initiation, and written informed consent was obtained from all study participants.

Assessments. ***Clinical.*** Motor disease severity was measured with the Unified Parkinson's Disease Rating Scale (UPDRS) Part III and the Hoehn & Yahr (H&Y) Scale. Depression symptom severity was assessed with the 15-item Geriatric Depression Scale, with a cutoff score of ≥5 indicating clinically significant depressive symptoms in patients with PD.[18] Psychosis and apathy were assessed with UPDRS part I items (any positive score was considered to indicate presence of psychosis or apathy).

Neuropsychological assessment. At baseline and at each follow-up visit, a battery of cognitive tests was administered to participants by trained research personnel. The neuropsychological assessment was previously described as part of the recommended standard battery of cognitive tests for patients with PD enrolled in cognitive research studies at Udall Centers.[19] Specific cognitive tests were as follows: global cognitive abilities, DRS-2; executive abilities/working memory, Letter-Number Sequencing and phonemic verbal fluency (FAS); memory, Hopkins Verbal Learning Test–Revised (HVLT-R); visuospatial function, Judgment of Line Orientation; and language, the short Boston Naming Test (BNT) and semantic verbal fluency (animals). For all tests, published norms were used to generate standardized scores.

Consensus cognitive diagnosis. Assignment of a cognitive diagnosis was made for each patient at baseline and at every annual or biannual visit during a consensus conference held every 6 months by movement disorders specialists affiliated with the Penn Udall Center. The consensus process involved multiple (5 on average) pairs of experienced physician raters reviewing demographic and available clinical data (including the clinician or patient impression of cognitive decline compared with premorbid state, the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale [a measure of functional abilities], and both raw and standardized scores from the aforementioned cognitive battery). The physician raters assigned patients a diagnosis of normal cognition, MCI, or dementia for each visit based on the available data and following the diagnostic criteria proposed by the MDS Task Forces for MCI (level 1 criteria)[4] and dementia.[20] For a given test, a standardized score ≥1.5 SD below the mean was considered impaired, although discretion was allowed. Raters were not blinded to previous years' cognitive diagnoses for a given patient. First, the raters within a pair reached agreement on all cases assigned to them. For cases with a between-pair discrepancy in diagnosis, an independent physician rater adjudicated. Between-pair interrater agreement over time was assessed in 137 cases assigned to 2 pairs. Interrater agreement between pairs of raters was high[21] (kappa = 0.80, 95% confidence interval = 0.70–0.90). A participant was discontinued from the study if assigned a diagnosis of dementia in 2 consecutive years; for the purpose of these analyses, this diagnosis was carried forward if the patient was still alive at the time that a future visit would have occurred.

Statistical analysis. Kaplan-Meier method was used to estimate the incident impairment probability (rate) from normal cognition to any cognitive impairment, as well as the progression rate from MCI to dementia. Cox regression models were used to determine predictors associated with the probability of progression from normal cognition to any cognitive impairment. These methods used all subjects in the sample and can appropriately account for censored (missing) observations (i.e., subjects who did not develop the event of interest during the study period or dropouts before the end of the study). Variables with p value ≤0.05 on bivariate Cox model analysis were included to build the final multivariate Cox models. Depression, psychosis, and apathy were entered as dichotomous variables. Since our study was exploratory rather than confirmatory, multiple testing adjustment was not performed.[22] Statistical significance was set at $p < 0.05$. All statistical tests were 2-sided. Analyses were conducted with SPSS 22.0 (SPSS Inc., Chicago, IL).

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RESULTS

Subject characteristics. Table 1 describes the baseline demographic, clinical, and cognitive data of all study participants. Figure e-1 on the *Neurology*® Web site at Neurology.org summarizes the cohort of participants at each follow-up point. At baseline, 141 participants were available for analysis. Sixty-eight participants were eligible for the year 6 follow-up visit at time of analysis, and 80.9% (55/68) were seen. Sixteen participants (11.3% of the cohort) died during the course of the study; 12/16 had been diagnosed with cognitive impairment prior to death. The mean (SD) years of follow-up for the entire cohort were 4.4 (1.4) years. One patient converted to impairment reverted back to normal for subsequent years, and was considered normal throughout the analysis.

Progression from normal cognition to cognitive impairment. Estimated cumulative progression rates from NC to any cognitive impairment based on the Kaplan-Meier analysis were 8.5% at year 1, 21.3% at year 2, 30.4% at year 3, 39.1% at year 4, and 47.4% at year 6 (table 2; figure 1). Regarding specific cognitive diagnoses, the estimated progression rates from NC to MCI were 7.8%,

Table 1 Baseline characteristics

Variables	Percentage or mean (SD; range)
Demographics	
Male	63.1
Age, y	68.6 (7.0; 62–73)
Education, y	16.5 (2.2; 12–20)
Clinical	
Disease duration, y	5.0 (4.4; 1–23)
Hoehn & Yahr stage	
≤1.5	14.1
2.0 (median)	56.7
≥2.5	29.1
UPDRS III motor score	19.9 (10.0)
Levodopa equivalent daily dose,[34] mg/d	462.4 (480.0)
Dopamine agonist equivalent daily dose, mg/d	137.8 (400.8)
Total levodopa equivalent daily dose, mg/d	670.7 (160.0)
Psychiatric	
GDS-15 score	2.3 (2.5; 0–10)
UPDRS apathy score, % positive	26.1
UPDRS psychosis score, % positive	29.7
Cognition	
DRS-2 (raw score)[a]	139.5 (2.7; 134–144)
DRS-2 standardized, age-adjusted score	11.5 (1.9)
Lexical fluency (FAS) total score	41.3 (15.9)
Animal fluency score	18.6 (4.5)
BNT score[b]	56.4 (4.0)
JLO score[c]	22.3 (5.4)
LNS score[d]	10.0 (2.4)
HVLT-R total free recall score[e]	21.9 (5.5)
HVLT-R delayed recall score[f]	6.8 (3.2)
HVLT-R retention percentage score	74.0 (28.7)
HVLT-R recognition[g]	10.8 (1.3)

Abbreviations: BNT = Boston Naming Test; DRS-2 = Dementia Rating Scale–2; GDS-15 = 15-item Geriatric Depression Scale; HVLT = Hopkins Verbal Learning Test–Revised; JLO = Judgment of Line Orientation; LNS = Letter-Number Sequencing; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] Maximum score = 144; [b] maximum score = 60; [c] maximum score = 30; [d] maximum score = 21; [e] maximum score = 36; [f] maximum score = 12; [g] maximum score = 12.

18.5%, 28.0%, 36.1%, and 43.0% over the same time period. The rates for progression to dementia at each time point over the course of the study were 0.7%, 3.5%, 7.5%, 12.9%, and 28.0%.

Progression from incident MCI to dementia. The number of incident MCI participants seen for follow-up visits from time of diagnosis of incident MCI were as follows: 34 at year 1, 30 at year 2, 11 at year 3, 5 at year 4, and 4 at year 5. Estimated cumulative progression rates for incident MCI cases to dementia based on the Kaplan-Meier analysis were 16.2% at year 1, 39.1% at year 2, 57.3% at year 3, 78.7% at year 4, and 100.0% at year 5 (figure 2).

Baseline predictors of progression from normal cognition to cognitive impairment. Baseline variables predicting progression to cognitive impairment are shown in supplementary table e-1. Male sex ($p = 0.02$), increasing H&Y score ($p < 0.001$), higher UPDRS motor score ($p < 0.001$), longer duration of PD ($p = 0.05$), and presence of depression ($p = 0.03$) all predicted progression from NC to cognitive impairment on bivariate analysis. Entering these 5 variables into a Cox proportional hazard model and controlling for baseline DRS-2 scores, male sex ($p = 0.02$), higher UPDRS motor score ($p < 0.001$), and lower baseline total DRS-2 score (<0.001) persisted in predicting future cognitive decline (table 3).

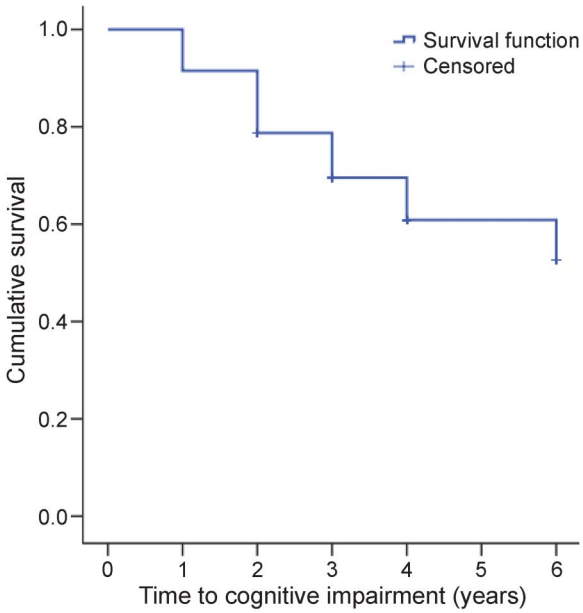
Neuropsychological test scores. To learn whether performance in specific domains of cognition predicted future cognitive decline, we evaluated the association of baseline performance on 8 cognitive test scores from 6 tests on future cognitive decline in a multivariate model controlling for significant variables from the bivariate analysis, including global cognition (i.e., DRS-2 raw scores). Specifically, we found that low baseline performances on FAS ($p < 0.001$), animal naming ($p = 0.009$), BNT ($p < 0.001$), LNS ($p = 0.003$), HVLT-R total recall ($p < 0.001$), and HVLT-R recognition discrimination ($p = 0.01$) were independent predictors of progression from normal cognition to cognitive impairment (table e-2).

Table 2 Progression rates to cognitive impairment by years of follow-up[a]

	Years of follow-up, %				
Group	1	2	3	4	6
Cognitive impairment	8.5	21.3	30.4	39.1	47.4
MCI	7.8	18.5	28.0	36.1	43.0
Dementia	0.7	3.5	7.5	12.9	28.0

Abbreviation: MCI = mild cognitive impairment; NC = normal cognition.
[a] Estimated percentage developing cognitive impairment based on Kaplan-Meier survival analysis. Eighteen participants had both MCI and dementia (diagnosed with MCI initially and subsequently with dementia). These people contributed to the analysis of both NC to MCI and NC to dementia. Thus, the sum of the progression rates to MCI and to dementia does not add up to progression rate to cognitive impairment in a given year.

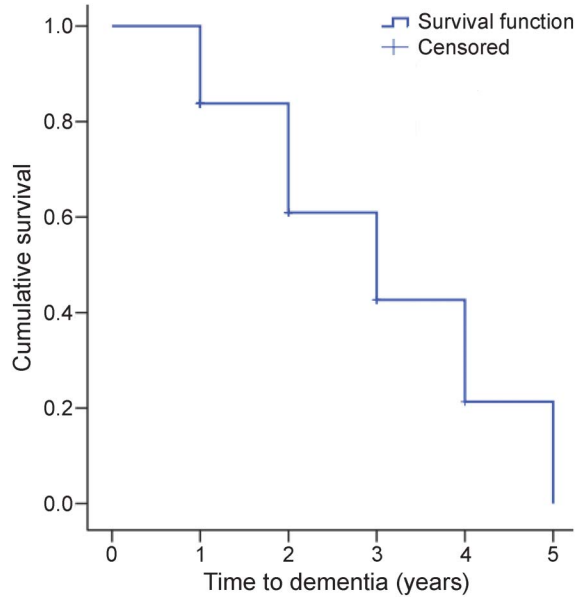
Figure 1 Kaplan-Meier survival curve for progression from normal cognition to any cognitive impairment



DISCUSSION The results of our study show that approximately half of patients with well-established PD with normal cognition develop cognitive impairment within 6 years of their baseline visit. In addition, patients newly diagnosed with MCI progress from MCI to dementia within 5 years, indicating that new-onset cognitive impairment in well-established PD represents prodromal dementia. This novel study reports on the longitudinal cognitive outcomes of a relatively large cohort of patients with PD with a consensus diagnosis of normal cognition at baseline, including outcomes for incident MCI. We demonstrated that cognitive impairment, including dementia, develops commonly and relatively quickly in patients with established PD with normal cognition.

Although stage and duration of disease varied among our participants, our findings are consistent with previous studies of cognitive function in PD, which have shown cross-sectional MCI prevalence rates of 25%–30%, frequent development of cognitive impairment in patients with early PD followed over a similar period of time, and high cumulative prevalence rates of dementia.[3,23] A previous smaller (n = 72) study examined PD-MCI prognosis and found that 62% of patients with MCI had developed PDD within a 4-year follow-up period, although that study, unlike ours, did not look at incident cases of MCI and thus the duration of MCI diagnosis was variable.[24] A recent study of patients with early PD and shorter follow-up (3 years) found that 27% of patients with MCI developed dementia during this time period, with older age and both attention and verbal memory deficits predicting decline.[7] Although it has been hypothesized that some MCI subtypes presenting early in the disease course may be stable and not progress to dementia,[25] our findings suggest that if a patient with PD develops incident MCI, progression to dementia may be universal within 5 years. Progression to dementia may be particularly rapid in older patients (the mean age of our cohort at baseline was 69 years), although surprisingly age was not a significant predictor, perhaps due to the narrow age range of our cohort. These findings are in contrast to those reported for MCI in the general population, in which the majority of patients will not progress to dementia even after 10 years of follow-up.[26]

Figure 2 Kaplan-Meier survival curve for progression from incident mild cognitive impairment to dementia



Using total DRS-2 score to control for global cognitive performance at baseline, demographic predictors of progression to cognitive impairment included male sex, consistent with the previously reported association between male sex and cognitive impairment in PD.[27] In addition, higher baseline UPDRS motor score predicted worse cognitive outcome, also consistent with previous studies showing that disease severity is associated with both PD-MCI and PDD.[28] Neuropsychiatric symptoms, including depression, apathy, and psychosis, have been shown to predict development of MCI in the general population,[29] but in our PD cohort, baseline neuropsychiatric symptoms alone did not predict progression to cognitive impairment. This finding could be a result of the limited battery of neuropsychiatric testing completed in this cohort.

It has been hypothesized that stable mild cognitive deficits in PD may represent a frontostriatal syndrome secondary to dopaminergic deficiency,[25] while progressive cognitive decline may be related to nondopaminergic (including cholinergic[30]), nonstriatal neuropathophysiologic changes. However, this hypothesis may be overly

Table 3 Cox regression model of factors predicting progression to cognitive impairment

Variable	Wald	*df*	Hazard ratio	95% CI of hazard ratio		*p* Value
				Lower	Upper	
Sex	5.755	1	0.467	0.251	0.870	0.02
Age	0.025	1	1.003	0.961	1.048	0.87
Duration of disease	<0.001	1	1.000	0.939	1.064	0.99
H&Y	1.308	1	1.450	0.767	2.740	0.25
UPDRS III motor	15.539	1	1.079	1.039	1.121	<0.001
GDS-15 score	1.836	1	1.073	0.969	1.189	0.18
DRS-2 total score	14.094	1	0.809	0.724	0.904	<0.001

Abbreviations: CI = confidence interval; DRS-2 = Dementia Rating Scale-2; GDS-15 = 15-item Geriatric Depression Scale; H&Y = Hoehn & Yahr; UPDRS = Unified Parkinson's Disease Rating Scale.

simplistic, and one previous study found that below-average performance in cognitive measures linked with widespread brain regions predicted more rapid cognitive decline and progression to PDD over a 3- to 5-year period.[8] Similarly, in a multivariable model controlling for clinical and demographic predictors of cognitive decline as well as baseline global cognitive performance (i.e., total DRS-2 score), we found that worse performance in multiple cognitive domains (i.e., verbal memory, executive abilities, working memory, and language) were independent predictors of progression to cognitive impairment. Given that baseline global cognitive performance (i.e., the DRS-2 score) also predicted future decline, routine screening with a global instrument may be as good for determining long-term clinical course as a more detailed neuropsychological battery.

Study limitations need mention. Our cohort was recruited from a single movement disorders center, was 99% Caucasian, had a mean education level of approximately 16 years, and had a narrow age range (25th to 75th percentile = 62–73 years), all reflective of the clinic population and study cohort specifically. Therefore, our results may not be generalizable to the PD community at large, and the narrow age range may explain discrepancies in our results compared to others listing age as a predictor of cognitive decline. Furthermore, since the currently accepted level II diagnostic criteria for MCI in PD (requiring 2 cognitive tests in each of the 5 cognitive domains) were only proposed in 2012,[4] we were unable to apply these criteria to our cohort (including MCI subtyping), as most of our participants were enrolled before this time point. Since we did not have the recommended 10 cognitive tests available for review, we may have underestimated the conversion rates from NC to cognitive impairment. Third, while all patients were classified as NC at baseline, the duration of disease before enrollment was variable, so we are not able to comment on the course of NC from disease onset. Fourth, the number of incident MCI cases with long-term follow-up from the time of MCI diagnosis was small (n = 37), so our findings of universal progression of incident MCI to dementia within 5 years in a well-established PD population needs validation in a larger cohort. Fifth, 20% of participants who should have contributed year 6 data dropped out of the study prior to this point. Sixth, we used brief or self-reported measures of apathy, psychosis, and depression, while other studies have used more detailed and more sensitive measures, and we did not examine all previous clinical or biological predictors of cognitive decline, such as gait impairment[31,32] and *APOE4* status.[33]

The results from this prospective study in a well-characterized cohort indicate a high risk of developing new-onset cognitive impairment, including dementia, in patients with well-established PD. Within this group, men and those with more severe motor disease and even subtle decreases in cognitive abilities (i.e., low normal performance) are at greatest risk of future cognitive decline. Ongoing and future studies that follow large samples of patients longitudinally from disease onset that include a comprehensive standardized battery of neuropsychological tests and that apply accepted diagnostic criteria for cognitive disorders in the setting of PD will fully elucidate the course of cognition in PD and risk factors that can predict decline. A more robust understanding of the nature of cognition in PD will improve clinical management and inform future trials of cognitive interventions.

AUTHOR CONTRIBUTIONS

H. Hurtig and A. Siderowf designed the study. K. Pigott and J. Rick performed study assessments. D. Weintraub, K. Pigott, J. Rick, and S. Xie analyzed the data. H. Hurtig, R. Akhtar, L. Chahine, A. Chen-Plotkin, N. Dahodwala, J. Duda, J. Morley, A. Siderowf, and D. Weintraub recruited participants, verified a PD diagnosis, recorded study data, or participated in the cognitive consensus process. K. Pigott and D. Weintraub drafted the manuscript. All authors edited the manuscript for accuracy and content.

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This Week's *Neurology*® Podcast

Longitudinal study of normal cognition in Parkinson disease **(see p. 1276)**

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the October 13, 2015, issue of *Neurology*. In the second segment, Dr. Matthew Barrett talks with Dr. Daniel Weintraub about his paper on the study of normal cognition in Parkinson disease. In our "What's Trending" feature of the week, Dr. Ted Burns interviews Mike Avery about happenings in the Beltway that are of interest to neurologists. In the next part of the podcast, Dr. Ted Burns focuses his interview with Dr. Steve on a Neurology Today® story about the uptick in cases of narcolepsy. Disclosures can be found at Neurology.org.

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