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UPDRS ACTIVITY OF DAILY LIVING SCORE AS MARKER OF PARKINSON'S DISEASE PROGRESSION

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Abstract

The Activities of Daily Living (ADL) subscore of the UPDRS captures the impact of Parkinson's Disease (PD) on daily function and may be less affected than other subsections by variability associated with drug cycle and motor fluctuations. We examined UPDRS mentation, ADL and motor subscores in 888 patients with idiopathic PD. Multiple linear regression analyses determined the association between disease duration and UPDRS subscores as a function of medication status at examination and in a subset of patients with multiple examinations. Independent of medication status and across cross-sectional and longitudinal analyses, ADL subscores showed a stronger and more stable association with disease duration than other UPDRS subscores after adjusting for age of disease onset. The association between disease duration and the motor subscore depended on medication status. The strong association between ADL subscore and disease duration in PD suggests that this measure may serve as a better marker of disease progression than signs and symptoms assessed in other UPDRS sections.

INTRODUCTION:

Accurate assessment of disease progression in Parkinson's disease (PD) is necessary to evaluate the impact of symptomatic and potential disease modifying treatments. The Unified Parkinson's Disease Rating Scale (UPDRS) is a widely used clinical tool that assesses functional status and motor performance.¹ Both activities of daily living (ADL; Part II) and motor (Part III) subsections have been studied psychometrically,²⁻⁴ showing good inter- and intra-rater reliability.⁵ Studies of early untreated and treated patients demonstrated changes in UPDRS subscores over time, although a comparison between ADL and motor subsections was not included.⁶⁻⁸

Levodopa treatment produces motor fluctuations that can influence performance on the motor section of the UPDRS. In contrast, ADL subscores are more likely to be independent of variations introduced by treatment status during assessment. Thus, we postulated that ADL subscores of the UPDRS would be a more reliable marker of disease progression. Using disease duration as an index of progression, we looked at UPDRS mentation, ADL, and motor subscores in relation to disease duration in 888 sequential patients evaluated at the University of Virginia Movement Disorders Program.

METHODS:

Patient Population:

Patients diagnosed with idiopathic PD referred to the subspecialty Movement Disorders clinic at the University of Virginia were enrolled in a clinical database. Patients were evaluated and diagnosed by a movement disorders-trained neurologist. Patients diagnosed with Parkinson's plus syndromes or drug-induced parkinsonism were excluded. Clinical diagnostic accuracy is 91% based upon autopsies of our patient population (G.F. Wooten, unpublished data). The database was screened for PD patients with complete data, which included an estimate of disease onset, disease duration, medication history for treatment of PD, medication status at the evaluation, and Parts I-III of the UPDRS.

We evaluated the correlation between disease duration and test scores using both a cross-sectional, "between subjects" model (evaluations of different patients at their initial visit) and a longitudinal "within subjects" model (sequential evaluations in the same patient over time). The former gains power from including a large number of cases, whereas the latter gains power from factoring out differences between patients. Ideally, the two models should converge on similar findings.

Statistical Methods:

Cross-sectional data: Cross-sectional data from the initial examinations of 888 PD patients were analyzed by multiple linear regression. The duration since onset of PD was treated as a surrogate for the progression of disease in the regression analysis. In addition to levodopa medication status ("on", "off", or not yet taking) at initial examination and the chronological age at onset of PD, ADL, motor, and mentation subscores were predictors of disease duration. The multivariate regression model was specified so that the individual relationships between disease duration and the predictor variables were free to change depending on medication status. Linear regression model parameters were estimated via ordinary least-squares, and the generalized F-test determined whether or not specific sets of regression coefficients were equal to zero. In cross-sectional and longitudinal analyses, confidence intervals were based on the Student-t distribution multiplier.

Longitudinal data: Longitudinal data of 162 PD patients with multiple examinations and who were either consistently "on" (n=128) or not yet taking (n=34) levodopa medication at each evaluation were analyzed by way of multivariate random coefficient regression (RCR). Disease duration was treated as a surrogate for the progression of disease in the regression analysis. In addition to levodopa medication status ("on" or not yet taking) and chronological age at onset of PD, ADL and motor function subscores were predictors of disease duration. The multivariate RCR model was specified so that the individual relationships between disease duration and the predictor variables were free to change depending on medication status. The regression parameters associated with the ADL and motor subscores were modeled as "random variables" so that individual regression coefficients for ADL and motor function were free to change. The RCR model parameters were estimated via restricted maximum likelihood, and the F-test test determined whether or not specific sets of regression coefficients were equal to zero.

Sensitivity-Analysis: An additional RCR longitudinal analysis assessed the sensitivity of ADL and motor subscores to detect the duration of PD. As predictors of the duration of PD, the RCR regression model included age at onset of PD, medication state ("on" or not yet taking levodopa), and a standardized version of ADL and motor subscores. Subscores were transformed to a common z-scale, with the resulting metric (standard deviation units) denoting the number of standard deviations that the raw (ADL/motor function) score

deviated from the average of the raw (ADL/motor function) scores in the positive or the negative direction. The multivariate RCR regression model was specified so that subject-specific slope parameter estimates were estimated for each individual, measuring the change in the disease duration (progression of disease) per unit change in the ADL and the motor function z-score. The assessment of the sensitivity of ADL and motor function z-scores to detect the progression of disease was based on several salient features of the distribution of the slope parameter estimates (e.g. central location, variability, and regression slope coefficient sign [+/-]). Analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary NC).

RESULTS:

One thousand ninety-five PD patients with initial evaluations were identified retrospectively from the database. Two-hundred seven patients were excluded because of incomplete data. The final sample of 888 cases consisted of 338 women (38%) and 550 men (62%), a ratio that is consistent male predominance in other series. The initial visit of these 888 patients served as the data set for the cross-sectional analysis. Mean age at onset was 58.2 years (range 28-88 years; $SD \pm 11$), with a mean disease duration of 7 years (range 1-30 years; $SD \pm 6$). Overall, 45% of the patients had disease duration of less than 5 years, with 75% less than 10 years. The mean total UPDRS score was 41.8 (range 2-131; $SD \pm 22.5$). The mean UPDRS motor subscore was 28.5 (range 2-90; $SD \pm 15.3$), the mean ADL subscore was 11.4 (range 0-40; $SD \pm 7.3$), and the mean mentation subscore was 1.9 (range 0-14, $SD \pm 2.2$). Nearly two-thirds of the patients were taking levodopa (586; 66%) with a mean dose of 632 mg/day (range 75-2250; $SD \pm 381$). Of the 888 initial evaluations, 404 patients were examined during the levodopa “on” state, 184 during the levodopa “off” state, and 300 patients were not yet taking levodopa. A subset of 162 patients that completed more than one annual evaluation in the same levodopa state (“on” or not yet taking levodopa) was used for longitudinal analyses.

Cross-sectional Results:

The scatterplots in Figure 1 depict the cross-sectional association between disease duration and ADL (top row), motor (middle row), and mentation (bottom row) subscores for patients in the levodopa “on” or “off” state, or not yet taking levodopa at initial examination. The plots reveal a stable, positive association between disease duration and ADL subscore across medication status. The cross-sectional association between disease duration and motor subscore depends on medication status, with a stronger association emerging for patients in the levodopa “off” state and weaker associations occurring for patients in the levodopa “on” state or not yet taking levodopa. The cross-sectional association between disease duration and mentation subscore is weak across all medication groups.

Because ADL and motor subscores correlate with each other and with disease duration, our multivariate regression models adjusted for age at disease onset and the patient’s medication status to determine the unique cross-sectional partial associations between disease duration and UPDRS subscores. The models included interaction terms so that the associations between disease duration and UPDRS subscores could depend on medication status. The cross-sectional partial association between disease duration and mentation subscore was non-significant across medication status, and the extra-sum-of-squares goodness of fit test indicated that mentation subscores did not provide significant explanatory information in the regression model ($p=0.44$). Thus, we dropped mentation as a predictor, proceeding with a reduced model that focused on the cross-sectional partial associations between disease duration and ADL and motor subscores.

Figure 2 (upper panel) plots the adjusted regression slope coefficients (with 95% confidence intervals) for the cross-sectional partial association between disease duration and UPDRS subscores. For patients examined in the levodopa “on” state, only the positive partial association between disease duration and ADL is significant (i.e., statistically greater than zero slope) ($p < 0.001$). For patients examined in the “off” state or not yet taking levodopa, the partial association between disease duration and ADL subscore and between disease duration and motor subscore are significant ($p < 0.05$). Examining each cross-sectional partial association across medication subgroups shows a statistically stronger positive slope coefficient between disease duration and ADL subscore for patients in the levodopa “on” state, and reduced, but equivalent, positive slope coefficients for patients “off” or not yet taking levodopa. The opposite is true for the partial association between disease duration and motor subscore, with a non-significant slope coefficient for patients “on” levodopa, and larger, but equivalent, positive slope coefficients for patients “off” or not yet taking levodopa.

Longitudinal Results.

The subset of patients used in the longitudinal analysis consisted of two groups, patients consistently evaluated at each examination in the levodopa “on” state ($n=128$) and patients not yet taking levodopa at each evaluation ($n=38$). Comparing these subgroups to patients excluded from the longitudinal analyses showed that the subgroup of included patients in the levodopa “on” state did not differ with respect to disease duration or age of onset from the excluded patients evaluated on just one occasion in the levodopa “on” state, but did show slightly lower scores on the motor (included = 23.0; excluded = 28.4) and ADL (included = 9.2; excluded = 12.7) subtests at the initial evaluation. The subgroup of included patients not yet taking levodopa did not differ from the excluded patients with respect to disease duration, age of onset, or motor subscores at the initial evaluation, but did show slightly lower scores on the ADL (included = 6.7; excluded = 8.8) subscore at the initial evaluation.

Results of the longitudinal analyses were broadly similar to those of the cross-sectional analyses (compare upper and lower panels from Figure 2). In the longitudinal analysis, intra-subject partial associations between disease duration and UPDRS subscores (ADL, motor) reflect associations over multiple examinations of the same patients over time (average duration between examinations: 2.2 years, range 0.3–6.8 years). In Figure 2 (lower panel), the slope coefficients for ADL and motor subscores regressed on disease duration and adjusted for age of onset are plotted for the two medication groups independently (leftmost columns) and combined (far right column). Regression slopes coefficient estimates in the lower panel of Figure 2 represent the restricted maximum likelihood estimate for the mean of the distribution of subject-specific regression slope coefficients in the study population. Combined, these regression coefficient estimates refer to the marginal regression coefficient estimates. For patients in the levodopa “on” state across evaluations, the intra-subject partial association (i.e., positive slope coefficient) between disease duration and ADL was statistically significant (i.e., greater than zero slope; $p < 0.0001$) after adjusting for age at disease onset and the interaction between medication status and the remaining variables in the model with respect to disease duration. In contrast, the intra-subject partial association between disease duration and motor subscore was not ($p = 0.89$). For patients not yet taking levodopa, the slope coefficients reflecting the intra-subject partial association between disease duration and ADL subscores and between disease duration and motor subscores were not statistically significant ($p = 0.13$ and $p = 0.23$ respectively).

Although the intra-subject partial association between ADL and disease duration was strong in the levodopa “on” state subgroup and not significant in the group not yet taking levodopa, the ADL slope coefficient did not differ between these groups ($p = 0.31$). The slope coefficients for the motor subscore and disease duration association did not differ across

medication status ($p = 0.32$). An extra-sum-of-squares goodness of fit test indicated that no significant explanatory information was lost by removing the medication status interaction terms from the original random coefficient regression model ($p=0.47$). Therefore, the overall slope coefficients for ADL and motor subscores are shown in the far right column of Figure 2 (lower panel) after removing the medication status interaction term. Again, the intra-subject partial association between disease duration and ADL subscore was statistically significant ($p < 0.001$), but the intra-subject partial association between disease duration and motor subscore was not.

To compare longitudinal associations, we focused on individual slope trajectories for ADL and motor subscores after raw scores were standardized to a common metric (z-score). In our longitudinal sample, we included patients with variable numbers of evaluations (minimum of 2) (Table 1). Figure 3 depicts the standardized subject-specific regression slope coefficients for ADL and motor subscores as a function of the number of repeat assessments. We collapsed across medication status given its non-significant impact in the prior longitudinal analysis. Ninety-eight percent of patients had regression slope coefficients that indicate a positive relationship between disease duration and the standardized ADL subscore (Table 1). In contrast, only about 58% of patients had slope coefficients that indicated a positive relationship between disease duration and the standardized motor subscores, whereas 42% indicated a negative relationship (Table 1). This highlights an unstable relationship between disease duration and motor subscores. Displayed in Table 2 are sets of descriptive statistics that describe several salient features of the distribution of the standardized ADL and motor subscore regression slope coefficients according to the number of repeated patient assessments. Most obvious is a larger regression slope coefficient characterizing the partial association between disease duration and ADL subscore relative to the partial association between disease duration and motor subscore, which remains consistent across the number of repeated assessments.

DISCUSSION

In this series of 888 patients with PD, cross-sectional analysis showed UPDRS ADL subscore had a stable, medication-independent, positive association with disease duration, whereas the association between disease duration and motor subscore clearly varied with medication status at the examination. The disease duration and motor subscore association was significant for patients examined in the levodopa “off” state or who were not yet taking levodopa, but not for patients examined in the levodopa “on” state. The longitudinal analysis of 162 patients observed multiple times in the same medication state supported the significant association between disease duration and ADL subscore, whereas the association between disease duration and motor subscore did not add unique information.

Three longitudinal series of treated patients have been reported previously.⁷⁻⁹ One did not employ the UPDRS, and of the others, one examined only motor subscores, and neither examined the ADL and motor subscores concurrently. Our finding of a strong cross-sectional and longitudinal association between ADL subscores and disease duration across treatment conditions after adjusting for age at disease onset suggests that this measure is sensitive to disease progression. One potential explanation is that treatment may affect motor signs without altering progressive functional decline. Alternatively, ADL subscores may be more sensitive to functional changes that are not necessarily reflected in motor subscores as the disease progresses. It is also likely that the ADL subscore is less affected by fluctuations in motor performance at the time of evaluation.

The positive association between disease duration and motor subscores was strongest and of similar magnitude to the association between disease duration and ADL subscore for

patients examined in the levodopa “off” state, but non-significant for patients examined in the levodopa “on” state. The longitudinal analysis revealed that the association between disease duration and motor subscores is relatively unstable, as roughly 42% of patients showed a negative regression slope coefficient, a value that was similar to the percentage of patients showing positive regression slopes. This highlights a difficulty with using motor subscores to track disease progression across patients as these scores are just as likely to improve as they are to worsen from one examination to another. In contrast, roughly 98% of patients showed a positive regression slope coefficient for the association between disease duration and ADL, and this percentage was consistent across different numbers of annual assessments (up to 4). Thus, for the vast majority of patients, changes in ADL subscores are less likely to fluctuate in opposite directions from one examination to another and may be a more reliable marker for disease progression.

A recent analysis of placebo-treated patients from the DATATOP study examined changes in ADL and motor subscores concurrently.⁶ Placebo-related improvement was seen in motor subscores from a subset of patients, but this was not reflected in changes in ADL subscores. Together with our results, this suggests that the ADL subscore derived from the patient’s report of function over the past week may be a more stable measure of disease progression than the motor subscore, which may be more affected by transient changes. The results also suggest that for patients examined in the levodopa “on” state at a single time point or longitudinally, the ADL subscore provides a more stable estimate of disease progression, whereas both the ADL and motor subscores contribute uniquely to the estimate of progression for patients examined at a single time point in the levodopa “off” state.

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Figure 1. Scatterplots of disease duration and ADL (top row), motor (middle row), and mentation (bottom row) subscores, across medication status (columns). Correlation coefficient (**r**) is provided in the lower right corner of each scatterplot.

Figure 2.

Upper panel (Cross-Sectional Data): Regression slope coefficients (with 95% confidence interval) for the cross-sectional association between disease duration and each of the predictors, ADL subscore and motor subscore, after adjusting for age at disease onset and medication status. Confidence interval bars that do not intersect with the zero slope line represent slope coefficients that are statistically significant at the $p < .05$ level.

Lower panel (Longitudinal Data): Marginal regression slope coefficients (with 95% confidence interval) for estimating the mean intra-subject partial association between disease duration and each of the predictors, ADL subscore and motor subscore, after adjusting for age at disease onset and medication status (left two columns). Confidence interval bars that do not intersect with the zero slope line represent slope coefficients that are statistically significant at the $p < .05$ level. Because medication status did not contribute to the intra-subject partial association between disease duration and UPDRS motor subscores, the far right column shows the overall marginal regression slope coefficients after removing the medication status interaction term.

Figure 3.

Standardized regression slope coefficients (with 95% confidence interval) for each subject's motor and ADL subscores included in the longitudinal analyses after adjusting for age at disease onset. The slope coefficients are plotted as a function of the number of repeat assessments each patient completed, including an "[2 - 4]" that collapses across the number of repeat assessments. The boxes in this figure identify the interquartile range of the empirical distribution, while the horizontal line in the interior of each box identifies the median of the distribution. Vertical lines identify the range of the distribution.

Table 1

Summarizes the percentage of patients who had a positive standardized subject-specific regression slope coefficient for the association of ADL or motor scores and disease duration as a function of the number the number of repeat UPDRS assessments.

# Repeated Assessments	UPDRS	# Positive Slope/Total # Slopes (%)
2 or 3 or 4	ADL Z Score	158/162 (97.5%)
2 or 3 or 4	Motor Z-Score	95/162 (58.6%)
2	ADL Z Score	77/78 (98.7%)
2	Motor Z-Score	45/78 (57.7%)
3	ADL Z Score	21/23 (91.3%)
3	Motor Z-Score	13/23 (56.7%)
4	ADL Z Score	60/61 (98.4%)
4	Motor Z-Score	37/61 (60.6%)

Table 2

Summary statistics for the empirical distribution of the standardized subject-specific regression slope coefficients.

UPDRS	# Repeated Assessments	n	Mean	Standard Deviation	Median	Minimum	Maximum	25 th Percentile	75 th Percentile
ADL	2 or 3 or 4	162	2.527	1.112	2.426	-0.167	6.841	1.834	2.984
Motor	2 or 3 or 4	162	0.302	1.955	0.344	-5.500	8.984	-0.762	1.385
ADL	2	78	2.496	1.011	2.357	-0.108	5.980	1.833	2.876
Motor	2	78	0.311	1.780	0.330	-3.628	8.984	-0.815	1.016
ADL	3	23	2.561	1.315	2.543	-0.108	5.652	1.956	3.030
Motor	3	23	0.503	2.483	0.430	-5.500	4.973	-0.609	1.767
ADL	4	61	2.555	1.170	2.547	-0.167	6.841	1.809	3.216
Motor	4	61	0.216	1.975	0.367	-3.996	4.815	-1.171	1.817