RESEARCH ARTICLE

Progression and Prognostic Factors of Motor Impairment, Disability and Quality of Life in Newly Diagnosed Parkinson's Disease

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ABSTRACT:

Objective: To determine progression and prognostic factors of progression rate of motor impairment, disability, and quality of life (QoL) in patients with newly diagnosed Parkinson's disease.

Methods: A group of 126 patients with newly diagnosed PD recruited from outpatient clinics participated in this 3-year prospective cohort study. Motor impairment was rated with the Unified Parkinson Disease Rating Scale Motor-Examination. Disability was rated using the Schwab and England Activities of Daily Living Scale, the AMC Linear Disability Score. QoL was assessed with the Parkinson's Disease Quality of Life questionnaire. Linear mixed model analyses were conducted to identify determinants of progression rate of motor impairment, disability, and poor QoL.

Results: Motor impairment progressed with 3 points per year. There was a slight progression of disability and QoL during 3 years of follow-up. Female sex was a prognostic factor for slower progression of motor impairment and QoL. Older age at onset showed to prognosticate faster progression of disability and impaired QoL. Furthermore, independent of follow-up time, older age at onset was associated with worse motor impairment; nondopaminergic reactive symptoms (Axial impairment) were associated with more disability and poorer QoL; comorbidity showed relation with disability and QoL but to a lesser extent; self-reported mood symptoms were associated with poorer QoL; and disease duration correlated with motor impairment.

Conclusions: Motor impairment, disability, and QoL of newly diagnosed Parkinson patients show progression in the first 3 years. Older age at onset predicts worse progression rate of disability and impaired QoL over time. Female sex predicts slower progression of motor impairment and less decline of QoL.

Key Words: Parkinson's disease; motor impairment; disability; quality of life; prognosis

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease after Alzheimer's disease[1,2] and will be an increasing problem in the near future.[3] Recently, several reviews identified older age at onset, postural instability and gait difficulty, bradykinesia, lack of tremor at disease onset, depression, and early cognitive impairment as prognostic factors for decline in motor impairment and/or disability.[4–6]

Schrag et al.[7] reported a mean annual progression rate of clinical disease severity ranging from 2.4% to 7.4%. The study showed that progression of motor impairment slows down with advancing disease stage and longer follow-up in contrast to the ongoing progression of disability. Another recently published report described a mean annual decline in the Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME) and the Hoehn and Yahr staging (HY) of 3.1% and 3.2%, respectively.[8] In this study age, age at onset, disease duration, and symptoms thought to be due to nondopaminergic brain structures were predictors of more motor impairment and disability. Both studies[7,8] described groups of prevalent PD patients introducing a selection of surviving PD patients and, so, an underestimation of the

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progression of PD. Although both studies are valuable, they can only provide prognostic information of patients from the moment they are included into the study.

The objective of this study is to prospectively describe the progression of motor impairment, disability, and quality of life (QoL) in a newly diagnosed hospital based cohort, which was followed up for 3 years. Furthermore, we explored the relative contributions of multiple potential predictors to progression in patients with PD.

Methods

Patients/Subjects

The study population comprised consecutive patients with newly diagnosed PD recruited between July 2002 and March 2005 from the neurology outpatient clinics of six general hospitals in the Netherlands, who were participants in a longitudinal research project investigating the course of functional status and its determinants in PD. All patients underwent baseline neurological and neuropsychological examinations, either in the hospital or at their home, between July 2002 and March 2005. Neuropsychological assessment was conducted within 1 to 4 weeks after the neurological examination. Neuropsychological outcome assessment was performed 3 years after baseline assessment and has been described elsewhere[9]; all other assessments were performed annually during the 3-year follow-up period. Annually evaluations were done by trained nurse practitioners and whenever possible by the same nurse practitioner at the same part of the day. A clinical diagnosis of PD based on standard criteria[10] was revalidated by the project neurologist through review of the medical records. Only patients whose diagnosis was confirmed were included in this analysis. A more detailed description of the project was published before.[9,11]

Written informed consent was obtained from all subjects after the nature of the study was fully explained. The study was approved by the local ethics committees of the participating hospitals.

Assessments

Baseline Patient and Clinical Characteristics

During the clinical examination information about demographic and clinical characteristics in terms of disease duration, initial symptoms, initial side of symptoms, types of therapy, and the use of drugs for PD were recorded (Table 1). We pooled different dopaminergic (levodopa and dopaminergic agonists) drugs in a L-dopa equivalent dose.[12]

Outcome Measures

The severity of extrapyramidal symptoms was rated using UPDRS-ME.[13] The UPDRS-ME was subdivided into two domains.[11,14] Motor subscore A ranged from 0 to 88 and represented relatively L-dopa responsive motor signs of PD. Motor subscore B ranged from 0 to 20 and represented relatively L-dopa nonresponsive motor signs of PD. Furthermore, the stage of disease was determined with the HY.[15]

Disability was evaluated using the Schwab and England Activities of Daily Living Scale (SE)[13] and the AMC Linear Disability Score (ALDS).[16] The ALDS item bank is developed to quantify functional status in terms of the ability to perform activities of daily living using an item response theory framework. The original units of the ALDS scale are (logistic) regression coefficients, expressed in logits. To make the results easier to interpret, the logit scores are linearly transformed into values between 10 and 90. The value 10 represents the lowest level and the value 90 the highest level of functional status possible. QoL was evaluated with a disease-specific instrument, the PD Quality of Life questionnaire (PDQL).[17]

TABLE 1. Baseline patient and clinical characteristics of the newly diagnosed PD patients

Patient and clinical variables	n = 126
Gender (M:F) (%)	56:44
Age at onset of symptoms (yr), mean (SD; range)	64.6 (10.4; 30.9–83.5)
Age at diagnosis of PD (yr), mean (SD; range)	65.9 (10.4; 32–84.6)
Age at examination (yr), mean (SD; range)	66.2 (10.4; 32.4–84.9)
Duration of symptoms at examination (yr), mean (SD; range)	20.0 (11.0; 4.7–83.9)
Symptoms at start of the disease, n (%)	
Tremor	58 (46)
Bradykinesia/rigidity	58 (46)
Tremor/bradykinesia/rigidity	10 (8)
Side of symptom onset start of the disease, n (%)	
Unilateral (R+L)	96 (45+51) [76 (36+40)]
Two sides asymmetric	20 (16)
Two sides symmetric	10 (8)
Therapy, n (%)	
No medication	38 (30)
Dopaminergic	81 (64)
Nondopaminergic	7 (6)
LED when receiving dopaminergic therapy mean (SD; range)	239.1 (118.7; 10–600)

SD, standard deviation; LED, L-dopa equivalent dose

Potential Prognostic Factors.

Based on review of the literature potential prognostic factors for progression of motor impairment, disability and QoL were chosen.[4–6] Age at onset, sex, disease duration, motor subscore A of the UPDRS-ME, motor subscore B of the UPDRS-ME, comorbidity, cognitive function, and affective symptoms measured at baseline were selected and used in the study analysis. The Cumulative Illness Rating Scale[18] was administered during history taking to assess comorbidity. We administered 17 neuropsychological tests to

TABLE 2. Progression of impairment, disability, and perceived QoL in newly diagnosed PD patients

	Baseline	Yr 1	Yr 2	Yr 3	*P**
UPDRS-ME, mean (SD)	17.2 (8.2)	21.3 (8.2)	23.8 (9.4)	26.0 (9.6)	<0.001
HY					
Median/mean (SD)	1/1.7 (0.7)	2/2.1 (0.6)	2/2.3 (0.5)	2/2.4 (0.5)	
I (%)	42.1	11.9	2.6	2.6	
II (%)	46.8	69.5	68.4	60	
III (%)	11.1	18.6	28.9	37.4	<0.001
SE, mean (SD)	90.0 (6.9)	89.2 (7.5)	86.5 (10.7)	82.0 (15.6)	<0.001
ALDS, mean (SD)	83.5 (9.1)	84.6 (7.9)	83.6 (10.5)	79.6 (16.4)	0.045
PDQL-total score, mean (SD)	146.9 (21.2)	147.3 (20.6)	142.9 (25.4)	141.3 (23.4)	<0.001
Parkinson symptoms	55.6 (8.3)	55.7 (7.8)	53.4 (9.7)	52.8 (8.7)	0.001
Systemic symptoms	26.5 (4.8)	27.0 (4.7)	26.4 (5.3)	26.3 (4.9)	0.359
Emotional function	28.9 (5.3)	28.4 (5.5)	27.7 (6.6)	27.0 (6.5)	0.001
Social function	36.0 (5.8)	36.2 (6.3)	35.3 (6.8)	35.2 (6.6)	0.126

*Linear mixed model, except for HY where Friedman test for ordinal variable was used.
UPDRS-ME, Unified Parkinson's Disease Rating Scale-Motor Examination; HY, Hoehn and Yahr scale; SE, Schwab and England activities of daily living scale; ALDS, AMC Linear Disability Scale; PDQL, Parkinson's Disease Quality of Life questionnaire; SD, standard deviation.

evaluate functions in five cognitive domains: attention and psychomotor speed, language, declarative memory, executive function, and visuospatial abilities as described by Muslimovic et al.[19] Cognitive dysfunction was considered to be present if performance on three or more neuropsychological tests was impaired. The Hospital Anxiety and Depression Scale (HADS), which has demonstrated validity in PD, was used as screening instrument of affective symptoms.[20,21]

Statistical Analysis

Demographic and clinical characteristics were summarized with descriptive statistics. The change in disease stage over time was analyzed using a Friedman test. Decline of motor impairment (UPDRS-ME), disability (SE and ALDS), and QoL (PDQL) over time was analyzed using linear mixed models. In addition, the impact of each baseline prognostic factors (age at onset, sex, disease duration, UPDRS-ME, comorbidity, cognitive function, and affective symptoms), including their interaction with follow-up time on health outcome, was assessed in separate mixed models. All identified significant prognostic variables and their interactions with time were offered to a multivariable model with a backward selection strategy. Significant interactions with time indicated prognostic factors for progression over time, whereas significant main effects were interpreted as associations independent of follow-up time. Two-tailed level of significance was set at $P = 0.05$. In view of the explorative nature of this study, we did not correct for multiple comparisons.[22] All analyses were performed in SPSS version 16 and R.

Results

Characteristics

Between July 2002 and March 2005, 133 patients from the neurology outpatient clinics of six general hospitals in the Netherlands were included in our cohort, of which, six patients developed Parkinson's disease dementia and one multiple system atrophy. In total, 126 had a diagnosis of PD after 3 years or at the last visit before their loss of follow-up. Of this group loss to follow-up was 10 patients (six died and four did not want to participate anymore), they were included in the analysis up to the time they were last seen.

Patients (56% male) had a mean age at onset of 64.6 years, a mean age at examination of 66.2 years with mean disease duration of 20 months (Table 1). The patients lost to follow-up had longer disease duration on baseline, but there were no significant differences regarding age at onset, age at examination, age at diagnosis, sex, UPDRS-ME total score, and the use or amount of dopaminergic therapy.

Progression of Motor Impairment

The UPDRS-ME progressed significantly over time with a mean change over 3 years of 9.3 points (Table 2). The linear mixed model showed an annual change of 3.0 points per year (Table 3). The median HY stage stayed stable >3 years, although there was a statistically significant change (Table 2) in distribution over the three HY stages of patients included in our study.

The UPDRS-ME score was univariably associated with sex*year, age at onset, disease duration at baseline, and comorbidity as rated with the Cumulative Illness Rating Scale (Appendix Table A1). In a multivariable linear mixed model, women showed a less steep slope of progression as opposed to men, meaning the annual progression rate of UPDRS-ME was less in women. Furthermore, independent of follow-up time, older age at onset, and longer disease duration turned out to be associated with the level of UPDRS-ME (Table 4).

TABLE 3. Progression of impairment, disability, and perceived QoL in newly diagnosed PD patients estimated with a linear mixed model

Scale	Slope per year	*P*	95%CI	N observations
UPDRS-ME	3.0	<0.001	(2.5, 3.6)	472
SE	−2.7	<0.001	(−3.6, −1.9)	475
ALDS	−1.3	0.045	(−2.14, −0.14)	473
PDQL	−2.4	0.001	(−3.6, −1.3)	468
Parkinson symptoms	−1.2	0.001	(−1.8, −0.5)	468
Systemic symptoms	−0.2	0.359	(−0.5, 0.2)	468
Emotional function	−0.8	0.001	(−1.2, −0.3)	468
Social function	−0.4	0.126	(−0.8, 0.1)	468

Estimated mean change per year (slope), estimated by a linear mixed model, and its 95% CI.
UPDRS-ME, Unified Parkinson's Disease Rating Scale-Motor Examination; SE, Schwab and England activities of daily living scale; ALDS, AMC Linear Disability Scale; PDQL, Parkinson's Disease Quality of Life questionnaire.

Progression of Disability

The SE disability scale and the ALDS also changed with time, with a mean change over 3 years of −8.4 points and −4.2 points, respectively (Table 2). The linear mixed model showed an annual progression rate for the SE of −2.7 and the corresponding decrease in ALDS score was −1.3 points (Table 3). When dichotomizing the SE scale in below and above 70 points, 16% of patients had a score lower than 70 at the 3-year follow-up examination meaning dependency in daily life.

Age at onset*year, disease duration, motor subscore A and B, HADS score, cognitive function*year, and comorbidity*year were univariably associated with SE disability scale (Appendix Table A2). In the multivariable mixed linear model, older aged patients showed faster progression (steeper slope) during the follow-up.

TABLE 4. Prognostic factors for impairment, disability, and perceived QoL in newly diagnosed PD patients estimated with a linear mixed model

Domain and scale	Univariable model significant prognostic variables	Multivariable model prognostic variables	Coefficient	95% CI	*P*
Impairment					
UPDRS-ME	Sex*year, age at onset, duration, and CIRS	Sex (women)	2.03	(−1.13, 5.21)	0.206
		Sex*year	−1.32	(−2.45, −0.19)	0.022
		Age at onset	0.21	(0.1, 0.35)	<0.001
		Duration	0.13	(0.02, 0.24)	0.018
Disability					
SE	Age at onset*year, duration, motor subscore A[a] and B*year[b], CIRS*year, HADS, and cognitive status*year	Age at onset	0.26	(0.10, 0.43)	0.002
		Age at onset*year	−0.14	(−0.23, −0.05)	0.002
		Motor subscore B[b]	−1.77	(−2.22, −1.32)	<0.001
ALDS	Age at onset*year, duration, motor subscore A[5] and B[6], and CIRS[7]	Age at onset	0.01	(−0.01, 0.03)	0.366
		Age at onset*year	−0.01	(−0.02, −0.01)	<0.001
		Motor subscore B[b]	−0.19	(−0.26, −0.14)	<0.001
		CIRS	−0.10	(−0.14, −0.58)	<0.001
Quality of Life					
PDQL	Sex, age at onset, duration, motor subscore A[a] and B[b], CIRS, and HADS, interaction terms?	Sex (women)	−0.52	(−5.94, 4.89)	0.84
		Sex*year	2.81	(0.57, 5.04)	0.014
		Age at onset	0.48	(0.19−0.70)	0.001
		Age at onset*year	−0.14	(−0.25, −0.03)	0.011
		Motor subscore B[b]	−2.99	(−4.11, −1.88)	<0.001
		CIRS	−1.86	(−2.67, −1.04)	<0.001
		HADS	−1.50	(−1.82, −1.18)	<0.001

Baseline variables and their interactions with time in a linear mixed model.
[a]Score A is the sum of UPDRS-ME facial expression/tremor/rigidity/bradykinesia; considered relatively L-dopa responsive.
[b]Score B is the sum of UPDRS-ME items concerning speech and axial impairment (arising from chair/posture/postural stability/gait); considered relatively L-dopa non-responsive.
UPDRS-ME, Unified Parkinson's Disease Rating Scale-Motor Examination; SE, Schwab and England activities of daily living scale; ALDS, AMC Linear Disability Scale; PDQL, Parkinson's Disease Quality of Life questionnaire; CIRS, Cumulative Illness Rating Scale; HADS, Hospital Anxiety Depression Scale.

Furthermore, independent of follow-up time, higher motor subscore B was associated with the SE score (Table 4).

Age at onset*year, disease duration, motor subscore A and B, and comorbidity were univariably associated with a worse ALDS score (Appendix Table A3). In the multivariable model, age at onset showed a small but significant interaction with time indicating a faster progression of ALDS score over time (steeper slope) with older age at onset. Furthermore, independent of follow-up time, higher motor subscore B and higher level of comorbidity were associated with level of disability.

Course of Quality of Life

The PDQL total score and the subscores "Parkinson symptoms" and "emotional function" progressed significantly over time, with an average change over 3 years of 6.6 points, −3.2 points, and −2.2, respectively (Table 2). The model showed an annual deterioration rate for the PDQL-total score of −2.4 points. For the Parkinson symptom and emotional symptom subscale, these rates were −1.2 and −0.8, respectively (Table 3).

Sex, age at onset, disease duration, motor subscores A and B, HADS score, and comorbidity were univariably associated with PDQL total score (Appendix Table A4). These associations were largely confirmed in the multivariable model: women showed a less steep slope of progression as opposed to men, meaning the annual progression rate of PDQL total score was less in women. Patients with older age at onset had a higher annual progression rate (steeper slope) as opposed to patients with younger age at onset. Furthermore, independent of follow-up time, higher motor subscore B, higher HADS score, and more comorbidity showed association with lower PDQL total score (Table 4).

Discussion

In this study, we prospectively assessed the decline of motor impairment, disability, and QoL over a 3-year period in patients with newly diagnosed PD as we explored earlier with a baseline analysis.[9] Motor impairment progressed with three UPDRS-ME points per year. Disability also showed a small albeit significant decline during follow-up, whereas the level of QoL slightly deteriorated in the domains Parkinson symptoms and emotional functioning. Older age at onset predicted faster decline of disability and faster deterioration of QoL. Female sex predicted a slower progression of motor impairment and less decline of QoL.

The following associations independent of follow-up time were found: nondopaminergic reactive symptoms (axial impairment) and comorbidity were related to more disability and poorer QoL; affective symptoms were associated with poorer QoL; older age at onset was associated with worse motor impairment; self-reported mood symptoms were associated with poorer QoL; and disease duration correlated with motor impairment.

Although cognitive dysfunction is described in early PD, the clinical relevance of this finding is still a matter of debate.[9,23,24] Several systematic reviews highlighted the importance of cognitive dysfunction as an important prognostic factor for future functional health.[4–6] In contrast, we observed that cognitive status had no impact on functional outcomes when analyzed together with other prognostic factors. This finding is in line with earlier baseline analysis of our cohort. In that study, only performance on verbal fluency tasks was related to a disability measure.[9] A possible explanation for this contrast is that the reports included in the systematic reviews studied demented PD patients, conducted univariable analyses, whereas in this study self-reported measures of disability and QoL were employed in a sample with overall mild cognitive dysfunction, and the independent impact of multiple determinants was examined simultaneously.

The mean annual progression rate of 3 points on the UPDRS-ME is consistent with earlier findings.[7,8,25] Alves et al.[8] reported a mean annual change of 3.3 points on the UPDRS-ME in a prevalent population based cohort with a mean disease duration of 9.1 years at the beginning of the study and a follow-up of 8 years.[8] Schrag et al.[7] reported a mean annual progression of 3.3 points in a clinic based sample with a mean disease duration of 9.3 years at the beginning of the study and 1 year follow-up. So, it looks like that there is a constant progression of motor symptoms over time, although it is likely that the progression described in these prevalent cohorts are an underestimation of the real progression rate due to selection of survivors.

We reported a mean annual progression rate for SE of 2.7 points in a newly diagnosed group with a mean baseline score of 90.0. However, in our cohort, the fast majority of patients (85%) were still independent at the end of our follow-up. In a community-based study of prevalent patients with PD, there was a mean annual progression rate of 5.2 points at 1 year follow-up and 2.7 at 4 years follow-up (mean baseline score 81.7). Alves et al. described a mean annual progression rate of 3.6 points in a prevalent cohort of PD patients with a mean baseline score of 67.8. These results suggest that there may be different progression rates depending on the disease stage of the PD patients.[8]

There is an increasing number of longitudinal studies focusing on QoL as outcome parameter,[26–28] but only one research group has described the progression and prognostic factors of QoL in early PD.[29] Marras et al. describe a slight decline in physical and

mental component score of the SF-36 over 1.5–2 years time, although they question the clinical relevance of their findings. In this study, baseline depression and self-rated cognitive function turned out to be associated with the physical component score, whereas older age and worse activities of daily living at baseline were associated with the mental component score. Postural instability and gait difficulty were the only features that deteriorated concurrently with QoL.[29] This and our study identified nondopaminergic reactive symptoms and mood disturbances as relevant factors for QoL. It must be realized that QoL is also influenced by symptoms not assessed in recent studies.

There are indications of sex differences in PD, possibly related to different levels of circulating estrogens in men and women.[30,31] Recently, a study reported later age at onset, more often a tremor dominant form, and higher levels of striatal dopamine binding on DAT-scanning in women compared with men.[30] This suggests a more benign phenotype in women. We showed a slower progression of the UPDRS-ME and less progression of the PDQL total score in women when corrected for other variables. These results are in line with the practice parameter of the AAN[5] suggesting sex is a probable prognostic factor of motor progression, with women progressing slower. However, Shulman[31] showed that women report greater disability and perceived a more reduced QoL compared with men.[31] Also two other reviews[4,6] conclude there is still conflicting evidence on sex as a prognostic factor. The definitive answer for this ongoing debate is still to be found.

Strengths of this study are the relatively large PD prospective sample, measured early in the disease, a standardized assessment of motor function, affective status and functional capacity, the use of both disease-specific and generic measures of disability and QoL, the neuropsychological examination, and the fact that multiple potential explanatory factors were considered simultaneously in the analysis. Limitations of this study should also be recognized. First, the majority of patients in our study formed a clinic-based sample, which may be subject to selection bias. However, these patients were recruited from six different general neurological clinics and reflect our daily practice of PD care. Second, the changes of disability and QoL over time were only slight, so the clinical relevance of these progression rates remains a matter of debate. Third, we measured patients with and without symptomatic treatment and analyzed them together, although pragmatic, can be more difficult to generalize the found progression rates.

Motor impairment, disability, and QoL of newly diagnosed Parkinson patients show deterioration in the first 3 years. Older age at onset predicts faster progression of disability and poorer QoL over time. Female sex predicts slower progression of motor impairment and less decline of QoL. ■

Appendix

Participants of the CARPA-study Group: Janneke M. Stolwijk-Swuste, Anita Beelen, Frans Nollet, Gaby M. van Dijk, Bart Post, Rob J. de Haan, Johannes D. Speelman, J. Dekker, and Guus J. Lankhorst.

TABLE A1. Baseline factors associated with greater impairment (UPDRS–ME) during follow-up

Scale	Baseline variable	Coefficient	P	95%CI	
UPDRS–ME	Age at onset	0.20	0.001	0.09	0.32
Univariable analysis	Age at onset *year	−0.02	NS	−0.07	0.04
	Duration	0.12	0.036	0.01	0.24
	Duration*year	−0.01	NS	−0.06	0.04
	Motor subscore A[a]	*1.45*	*<0.001*	*1.29*	*1.62*
	*Motor subscore A*year*	*−0.22*	*<0.001*	*−0.31*	*−0.13*
	Motor subscore B[b]	*2.87*	*<0.001*	*2.33*	*3.41*
	*Motor subscore B*year*	*−0.44*	*0.001*	*−0.69*	*−0.18*
	HADS	0.04	NS	−0.29	0.26
	HADS*year	−0.05	NS	−0.13	0.03
	Cognitive status	−2.26	NS	2.67	5.40
	Cognitive status*year	−1.35	0.080	−2.87	0.16
	CIRS	0.44	0.028	0.05	0.83
	CIRS*year	−0.08	NS	−0.26	0.11
	Sex (women)	2.03	NS	−1.29	5.36
	Sex*year	−1.30	0.025	−2.42	−0.17

Baseline variables and their interactions with time in a linear mixed model univariable analysis; underlined variables are significantly associated with the outcome, *cursive* variables are significant in univariable analysis but left out of the multivariable mixed linear model because of colinearity.
[a]Score A is the sum of UPDRS–ME items concerning facial expression, tremor, rigidity, bradykinesia; these are considered relatively L–dopa responsive.
[b]Score B is the sum of UPDRS–ME items concerning speech and axial impairment (arising from chair, posture, postural stability, and gait); these are considered relatively L–dopa nonresponsive.
UPDRS–ME, Unified Parkinson's Disease Rating Scale motor examination; HADS, Hospital Anxiety Depression Scale; CIRS, Cumulative Illness Rating Scale; NS, nonsignificant.

TABLE A2. Baseline factors associated with greater disability (SE) during follow-up

Scale	Baseline variable	Coefficient	P	95%CI	
SE	Age at onset	0.09	NS	−0.06	0.23
univariable analysis	Age at onset*year	−0.14	0.001	−0.21	−0.06
	Duration	−0.17	0.016	−0.30	−0.03
	Duration*year	0.04	NS	0.04	0.11
	Motor subscore A[a]	−0.34	0.012	−0.61	−0.08
	Motor subscore A*year	−0.07	NS	−0.07	0.08
	Motor subscore B[b]	−0.95	0.007	−1.63	−0.26
	Motor subscore B*year	−0.49	0.011	−0.86	−0.11
	HADS	−0.24	0.023	−0.45	−0.03
	HADS*year	0.05	NS	−0.06	0.17
	Cognitve status	0.94	NS	−3.05	4.93
	Cognitive status*year	−2.39	0.035	−4.61	−0.18
	CIRS	0.11	NS	−0.37	0.59
	CIRS*year	−0.32	0.016	−0.58	−0.06
	Sex (women)	−1.13	NS	−4.20	1.95
	Sex*year	0.92	NS	−0.79	2.62

Baseline variables and their interactions with time in a linear mixed model univariable analysis; underlined variables are significantly associated with the outcome.
[a]Score A is the sum of UPDRS–ME items concerning facial expression, tremor, rigidity, bradykinesia; these are considered relatively L–dopa responsive.
[b]Score B is the sum of UPDRS–ME items concerning speech and axial impairment (arising from chair, posture, postural stability, and gait); these are considered relatively L–dopa nonresponsive.
SE, Schwab and England Disability Scale; HADS, Hospital Anxiety Depression Scale; CIRS, Cumulative Illness Rating Scale; NS, nonsignificant.

TABLE A3. Baseline factors associated with greater disability (ALDS) during follow-up

Scale	Baseline variable	Coefficient	P	95%CI	
ALDS	Age at onset	−0.02	NS	−0.05	0.00
univariable analysis	Age at onset*year	−0.01	0.002	−0.02	−0.01
	Duration	−0.02	0.036	−0.03	0.00
	Duration*year	0.00	NS	−0.01	0.01
	Motor subscore A[a]	−0.06	<0.001	−0.08	−0.03
	Motor subscore A*year	−0.01	NS	−0.03	0.00
	Motor subscore B[b]	−0.29	<0.001	−0.35	−0.23
	Motor subscore B*year	−0.03	NS	−0.08	0.01
	HADS	−0.02	NS	−0.05	0.00
	HADS*year	0.00	NS	−0.01	0.01
	Cognitve status	0.43	NS	−0.03	0.89
	Cognitive status*year	0.13	NS	−0.12	0.38
	CIRS[5]	−0.18	<0.001	−0.23	−0.13
	CIRS*year	−0.02	NS	−0.05	0.01
	Sex (women)	−0.30	NS	−0.67	0.07
	Sex*year	0.12	NS	−0.07	0.31

Baseline variables and their interactions with time in a linear mixed model univariable analysis; underlined variables are significantly associated with the outcome.
[a]Score A is the sum of UPDRS–ME items concerning facial expression, tremor, rigidity, and bradykinesia; these are considered relatively L–dopa responsive.
[b]Score B is the sum of UPDRS–ME items concerning speech and axial impairment (arising from chair, posture, postural stability, and gait); these are considered relatively L–dopa nonresponsive.
ALDS, AMC Linear Disability Score; HADS, Hospital Anxiety Depression Scale; CIRS, Cumulative Illness Rating Scale; NS, nonsignificant.

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TABLE A4. Baseline factors associated with lower quality of life (PDQL) during follow-up

Scale	Baseline variable	Coefficient	P	95%CI	
PDQL	Age at onset	0.02	NS[6]	−0.37	0.41
Univariable analysis	Age at onset*year	−0.13	0.025	−0.24	0.02
	Duration	−0.54	0.001	−0.84	−0.23
	Duration*year	0.04	NS	−0.06	0.14
	Motor subscore A[a]	−1.10	<0.001	−1.50	−0.67
	Motor subscore A*year	0.05	NS	−0.23	0.34
	Motor subscore B[b]	−3.78	0.005	−5.18	−2.38
	Motor subscore B*year	0.18	NS	−0.36	0.71
	HADS	−1.77	<0.001	−2.14	−1.39
	HADS*year	0.13	NS	−0.02	0.29
	Cognitve status	−9.35	NS	−19.50	0.84
	Cognitive status*year	−1.69	NS	−1.14	4.54
	CIRS	−2.72	<0.001	−3.71	−1.72
	CIRS*year	0.19	NS	−0.18	0.54
	Sex (women)	−2.86	NS	−11.03	5.31
	Sex*year	2.54	0.029	0.26	4.84

Baseline variables and their interactions with time in a general mixed linear model univariable analysis; underlined variables are significantly associated with the outcome.
[a]Score A is the sum of UPDRS–ME items concerning facial expression, tremor, rigidity, and bradykinesia; these are considered relatively L–dopa responsive.
[b]Score B is the sum of UPDRS–ME items concerning speech and axial impairment (arising from chair, posture, postural stability, and gait); these are considered relatively L–dopa nonresponsive.
PDQL, Parkinson's Disease Quality of Life questionnaire; HADS, Hospital Anxiety Depression Scale; CIRS, Cumulative Illness Rating Scale; NS, nonsignificant.

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