Paper III

Progression of motor impairment and disability in Parkinson disease

A population-based study

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Abstract—*Objective:* To investigate risk factors and the rate of progression of motor symptoms and disability in a population-based cohort of patients with Parkinson disease (PD). *Methods:* In all, 232 patients with PD, derived from a community-based prevalence study, were followed prospectively over an 8-year period. Follow-up examinations were done 4 and 8 years after baseline, and 144 patients participated in at least one follow-up examination. Information on motor function and disability was obtained using the Unified Parkinson Disease Rating Scale (UPDRS), the Hoehn and Yahr staging, and the Schwab and England score. Population-averaged logistic regression models were used to describe annual disease progression and to analyze the influence of potential risk factors on functional decline. *Results:* We found a similar mean annual decline in the UPDRS motor score and the Hoehn and Yahr staging of 3.1% and 3.2%, respectively. Also the UPDRS Activity of Daily Living (ADL) score and the Schwab and England scale changed similarly, with 3.5% and 3.6% per year, respectively. Age, age at onset, disease duration, and excessive daytime somnolence at baseline were strong and independent predictors of greater impairment in motor function and disability. Cognitive impairment at baseline predicted higher disability and higher Hoehn and Yahr scores. Time by age-at-onset interactions were found for the UPDRS motor score and the Hoehn and Yahr staging. *Conclusions:* Motor function and disability worsened significantly with time, and to a similar extent. Age, age at onset and disease duration, as well as symptoms thought to be due to involvement of non-dopaminergic brain structures, are predictors of more impaired motor function and disability. However, age at disease onset was the main predictor of motor decline in our cohort, indicating a slower and more restricted pathologic disease process in patients with young-onset PD.

NEUROLOGY 2005;65:1436–1441

Due to the lack of in vivo biomarkers in Parkinson disease (PD) and the current limitations of neuroimaging methods to measure pathologic changes in nondopaminergic brain structures, clinical assessment using valid and reliable rating scales remains the gold standard in charting the course of the disease.[1]

However, prospective clinical investigations of disease progression, particularly in population-based cohorts, are still limited and have provided contradictory results on many potential risk factors of functional decline in PD.[2] There are several methodologic differences that may contribute to this variation. First, short follow-up of patients may lead to imprecise estimates of both predictors and rate of motor impairment and disability in a disease that progresses rather slowly over several years. Also, other types of Parkinsonism may clinically overlap with PD and thus not necessarily be distinguished before several years of disease duration. Second, due to heterogeneity within the PD group, progression rates and prognostic factors may vary between different subgroups of patients with PD. For example, results from clinic-based studies, usually comprising younger and quite well-functioning patients, are expected to be different from those in older, disabled PD patients living in nursing homes. Finally, variation in rates of progression, as well as conflicting results on prognostic factors, may also be related to the use of different outcome measurements. In addition, there is a lack of information on whether neuropsychiatric problems like fatigue, insomnia and excessive daytime somnolence, all shown to be frequent in patients with PD,[3,4] may predict future motor impairment or disability.

Hence, there is need for prospective long-term studies in representative, well-defined cohorts using standardized rating scales to provide valid information on prognostic factors and progression of functional decline in patients with PD. We therefore followed prospectively a community-based cohort of patients with PD over an 8-year period. The aims of the present study were to estimate the rate of progression in motor function and disability, and to ex-

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Disclosure: The authors report no conflicts of interest.

Received June 7, 2005. Accepted in final form July 20, 2005.

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plore the influence of several demographic and clinical features on functional decline in patients with PD.

Methods. *Study population.* In 1993, a prevalence study of PD was conducted in Rogaland County in the western part of Norway, comprising nine municipalities with 220,000 inhabitants. Patient recruitment has been published previously in detail.[5] After extensive search in hospital files and assessment of information from all available sources in the study area (general practitioners, nursing homes, district nurses, and health visitors), over 400 subjects were evaluated clinically by neurologists from the study group between September 1992 and May 1993. To achieve a total ascertainment of cases, patients not able to visit the outpatient clinic were examined at their homes or nursing homes. In total, 245 patients were diagnosed with clinical definite, probable, or possible PD according to published criteria.[6] The corresponding crude prevalence rate for PD was 110.9 per 100,000 inhabitants at January 1, 1993.[5] Patients were followed prospectively and re-evaluated after 4 and 8 years. Structural brain imaging (CT or MRI) was carried out in most patients, and only patients whose diagnosis of clinical PD was confirmed throughout the follow-up period were included in this study. To date, a subgroup of 22 patients has been assessed neuropathologically after they provided written informed consent. In all patients, neuron loss and α-synuclein-positive Lewy bodies in the surviving neurons of substantia nigra were found, thus confirming the clinical diagnosis of PD.

Of the 245 patients at baseline, seven were not able or refused to participate, and six patients were later during follow-up rediagnosed as not suffering from PD and excluded from the study. The remaining 232 patients were followed prospectively and invited by letter to participate in re-evaluation in 1997. During the first 4 years of follow-up, 81 patients had died, one person had moved abroad, and six patients refused participation in the examination in 1997. Thus, 144 patients were eligible for re-evaluation in 1997. Between 1997 and 2001, further 55 patients had died. A total of 89 patients were therefore available for evaluation in 2001.

Study design and patient evaluations. All patients were interviewed and examined by neurologists and psychiatrists from the study group. The same standardized examination and questionnaires were used in 1993, 1997, and 2001. Information on demographic variables, disease history, and drug treatment was obtained in semistructured interviews at each study visit. The Unified Parkinson Disease Rating Scale[7] (UPDRS) motor score (part III: 27 items, range 0-108) and the Hoehn and Yahr staging[8] were used to assess severity of motor symptoms. Disability was measured by the UPDRS ADL score (part II: 14 items, range 0-56) and the Schwab and England scale.[9] Disease subtype of the individual patient was classified into tremor-dominant (TD), postural-instability gait difficulty (PIGD), and indeterminate according to the dominance of motor symptoms in the UPDRS ADL and motor subscores, following a method described in previous studies.[10] Symptoms of depression were assessed by the Montgomery and Aasberg Depression Rating Scale (MADRS).[11] For assessment of cognitive impairment, both patients and caregivers were interviewed. The diagnosis of dementia was based on information obtained in semistructured interviews according to DSM-III-R criteria and the Mini-Mental State Examination (MMSE).[12,13] At follow-up visits, the Dementia Rating Scale (DRS)[14] was also administered and patients with an MMSE score of 16 or more underwent neuropsychological examinations. Details on the diagnostic assessment of dementia have been published previously.[15] Patients reporting nighttime sleep problems or using sleeping pills were deemed to have insomnia. For diagnosis of daytime somnolence, frequency and duration of sleeping periods during daytime were evaluated. Patients were classified as suffering from excessive daytime somnolence (EDS) when they slept more than 2 hours a day or fell asleep three times or more during daytime.[4] Classification of fatigue has been described previously and was based on a combination of parts from the Nottingham Health Profile (NHP) and a seven-point rating scale.[3,16] Patients who reported both lack of energy in the NHP and scored 4 or more on the seven-point rating scale were classified to have fatigue. In 2001, fatigue was also assessed by the Fatigue Severity Scale (FSS).[17]

Statistical analysis. The software programs SPSS 11.0 (SPSS, Chicago, IL) and STATA (StataCorp LP) were used for statistical analysis. Comparison of means for continuous variables was performed by using Mann-Whitney *U* test. Differences in proportions for categorical variables were analyzed by χ^2 tests.

Population-averaged regression models for correlated data (GEE)[18] were used to study the relationship between motor function (measured by the UPDRS motor subscore [part III] and the Hoehn and Yahr staging) and disability (measured by the Schwab and England score and the UPDRS ADL subscore [part II]) as dependent variables and various potential predictors of functional decline. The relationship between functional impairment during follow-up and the following baseline variables were analyzed in each regression model: age at onset, sex, disease duration, levodopa dose, disease subtype (TD, indeterminate subtype, PIGD), cognitive impairment according to MMSE and DSM-III-R criteria (dementia present or absent), depressive symptoms measured by MADRS, insomnia (present or absent), EDS (present or absent), and fatigue (present or absent). For all baseline variables, the interactions with follow-up time, when significant, were included in the model. In a second model, the analysis was repeated using age at baseline instead of disease duration, with all other variables remaining unchanged. Two-tailed *p* values less than 0.05 were considered significant.

Table 1 *Demographic and clinical characteristics of the study population at baseline and follow-up visits*

	Baseline	4-year visit	8-year visit
n	232	144	89
Age, y	73.5 (8.5)	74.4 (8.0)	76.1 (8.4)
Age at onset, y	64.4 (9.8)	61.8 (9.5)	59.4 (9.7)
Disease duration, y	9.1 (5.7)	12.7 (5.0)	16.8 (4.8)
UPDRS ADL score	14.5 (8.9)	18.6 (10.2)	25.2 (11.0)
UPDRS motor score	28.5 (15.8)	33.4 (21.8)	47.1 (20.7)
Hoehn and Yahr stage	2.8 (1.1)	3.2 (1.1)	3.4 (1.1)
Schwab and England score	67.8 (23.2)	58.8 (27.1)	55.6 (24.8)
MMSE score	24.4 (6.8)	23.3 (8.4)	18.7 (10.0)
MADRS score	8.1 (6.3)	4.9 (6.2)	8.2 (7.5)
Levodopa dose, mg/d	490 (247)	626 (378)	640 (420)

Values are means (SD), all available data included.

UPDRS = Unified Parkinson Disease Rating Scale; ADL = Activity of Daily Living; MMSE = Mini-Mental State Examination; MADRS = Montgomery and Aasberg Depression Rating Scale.

Results. Of the 232 patients originally derived from a population-based prevalence study, 144 were re-examined after 4 years of follow-up and 89 patients completed all three study examinations. Demographic and clinical characteristics of the study population at baseline and follow-up visits are given in tables 1 and 2.

Motor function. Both the UPDRS motor score ($p < 0.001$) and the Hoehn and Yahr staging ($p < 0.001$) progressed over time, with annual changes (slopes) of 3.3 points (range 0 to 108; 3.1%) and 0.16 points (range 0 to 5.0; 3.2%), for patients with mean age at onset (62 years).

The only interactions found were for time by age at onset, both for the UPDRS motor score ($p = 0.006$) and the Hoehn and Yahr staging ($p < 0.001$), with a steeper slope for higher age at onset. For the UPDRS motor scale, the slope was 2.6 points (2.4%) per follow-up year for patients 50 years old at onset and 3.8 points (3.5%) per year of follow-up for patients 70 years old at disease onset (figure). For the Hoehn and Yahr staging, these figures were 0.11

Table 2 *Demographic and clinical data at baseline and follow-up visits in a population-based cohort of patients with PD*

	Baseline	4-year visit	8-year visit
All patients	232	144	89
Male	114 (49.1)	64 (44.4)	38 (42.7)
Female	118 (50.9)	80 (55.6)	51 (57.3)
Disease subtype			
Postural instability gait difficulties motor subtype	150 (64.7)	107 (74.8)	79 (88.8)
Tremor-dominant subtype	44 (19.0)	25 (17.5)	5 (5.6)
Indeterminate	38 (16.4)	11 (7.7)	5 (5.6)
Treatment			
Levodopa	224 (96.6)	140 (97.2)	83 (93.3)
Dopamine agonist	52 (22.4)	25 (17.4)	27 (30.3)
Anticholinergics	4 (1.7)	2 (1.4)	0
Dementia diagnosis*	61 (26.3)	57 (39.9)	53 (59.6)
Excessive daytime somnolence	35 (17.7)	41 (32.8)	40 (44.9)
Fatigue	100 (44.1)	51 (45.9)	42 (54.5)
Insomnia	136 (58.9)	76 (53.5)	50 (56.2)

Values represent numbers (% of assessed patients); all available data included.

* According to DSM-III-R criteria.

points (2.2%) for patients 50 years old at onset and 0.20 points (3.9%) for patients with an age at onset at 70 years. The predicted time for progressing one Hoehn and Yahr stage (e.g., from stage 2.0 to 3.0) is thus 9.3 years for patients with disease onset at 50 years, 6.3 years for patients aged 62 at disease onset, and 5.1 year for patients with onset of the disease at 70 years.

In addition, several baseline variables were associated with more impaired motor function during follow-up as shown in table 3, although they were not significantly associated with more rapid motor decline. Baseline variables that were not associated with higher scores in the UPDRS motor part and Hoehn and Yahr staging during follow-up were sex, disease subtype, MMSE scores, depressive symptoms (measured by MADRS), insomnia, and fatigue.

When the analysis was repeated using age at baseline instead of disease duration, no significant time interactions were found. Both the UPDRS motor score and the Hoehn and Yahr staging still progressed significantly with time, with annual slopes of 3.3 and 0.16 points. Baseline variables that were significantly associated with higher levels of motor impairment during follow-up were almost identical with those found in the main model.

Disability. The UPDRS ADL score ($p < 0.001$) and the Schwab and England scale ($p < 0.001$) also changed with time, indicating increasing disability during follow-up. The mean annual increase in the UPDRS ADL score was 1.9 points (0 to 56; 3.5%), and the corresponding decrease in the Schwab and England score was 3.6 points (0 to 100; 3.6%).

Age at onset ($p < 0.001$), disease duration ($p < 0.001$), MMSE score ($p < 0.05$ and $p < 0.001$) and EDS ($p = 0.005$ and $p < 0.05$) at baseline were associated with greater disability measured by both UPDRS ADL and Schwab and England scores at follow-up examinations (table 4). In addition, higher UPDRS ADL scores during follow-up were also predicted by higher MADRS scores at baseline ($p < 0.05$), and higher Schwab and England scores were also related to higher levodopa doses ($p < 0.05$) at baseline. However, none of these baseline features interacted significantly with time. This is also true for the additional analysis, in which age at baseline ($p < 0.001$) predicted more impaired disability during follow-up, without any time interactions found. In both models, sex, disease subtype, dementia diagnosis, insomnia, and fatigue at baseline were not associated with higher disability scores during follow-up.

Discussion. In the present study we prospectively assessed the rate and predictors of functional decline over at average 6.5 years in a representative cohort of patients with PD. Although a slow progression is expected in the disease, our finding of similar annual changes in severity of motor symptoms and disability of 3.1% to 3.6% with four different instruments is new and remarkable. Several baseline variables, particularly those that may result from pathologic changes in nondopaminergic pathways (such as cog-

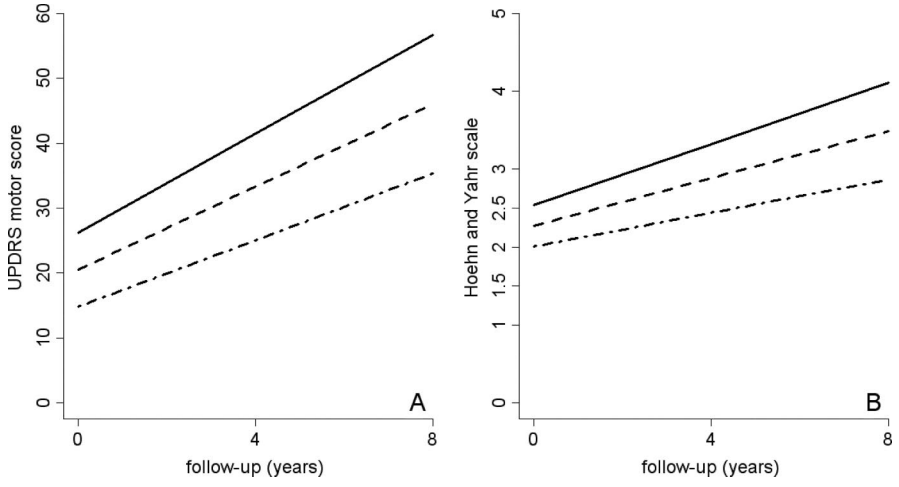

Figure. Motor decline in patients with PD. Age at onset-dependent rates of disease progression measured by the Unified Parkinson Disease Rating Scale motor score (A) and the Hoehn and Yahr scale (B). For all continuous covariates, mean values were used. For categorical covariates, the following values were used: female sex, tremor-dominant PD type, no dementia, insomnia, excessive daytime somnolence, or fatigue.

Table 3 *Baseline factors associated with greater impairment of motor function during follow-up*

	Unified Parkinson Disease Rating Scale motor scale		Hoehn and Yahr staging	
Baseline variable	Difference in score	*p* Value	Difference in score	*p* Value
Age at onset*	0.57	<0.001	0.027	<0.001
Age†	1.39	<0.001	0.072	<0.001
Disease duration	0.14	<0.001	0.007	<0.001
Excessive daytime somnolence	4.81	0.041	0.273	0.028
Dementia	NS		0.702	0.002
Levodopa dose	NS		0.001	0.001

* Significant time by age-at-onset interactions were found for the Unified Parkinson Disease Rating Scale motor score ($p = 0.006$; estimate 0.06; 95% CI 0.02 to 0.11) and the Hoehn and Yahr staging ($p < 0.001$; estimate 0.004; 95% CI 0.002 to 0.007).
† Derived from supplemental analysis.

nitive impairment, depression and EDS), were associated with more impaired function during follow-up. However, the patient's age at onset appears to be the most important predictor of motor decline in our cohort.

The use of four different clinical measurement instruments of motor function and disability is one strength of this study, in addition to the application of a population-based patient cohort and the prospective study design. Although the rather long intervals between examinations led to a substantial attrition rate due to death, loss to follow-up for other reasons was rare. The duration of follow-up in our study is the longest reported so far in population-based studies of disease progression, and may have contributed to the identification and exclusion of patients not suffering from PD. In the subgroup of subjects who underwent autopsy, all fulfilled neuropathological criteria for PD.

Cognitive impairment and EDS, both thought to reflect a more widespread cerebral disease with changes also in nondopaminergic brain systems,[4,19] were found to predict more severe motor impairment and disability. In addition, depressive symptoms predicted reduced activity of daily living in our cohort. This is in agreement with the current understanding of PD as a multisystem brain disorder in which neuropsychiatric problems have crucial impact on functioning and quality of life.[20-22]

The rate of motor decline in this patient cohort is comparable with findings from a recent neuroimaging study showing a 4.4% to 6.6% annual reduction in striatal 18^F fluorodopa uptake,[23] and similar to the 3.5% annual rate of loss of uptake in the caudate in patients with a diagnosis of PD for more than 4.5 years found in an earlier PET study.[24] However, the about 3% annual increase in the UPDRS motor score observed in our patient cohort was at least twice as high as reported in previous studies of clinical disease progression in PD using the same measurement instrument. Although the Hoehn and Yahr scale is a widely used and acknowledged instrument to assess the staging of motor symptoms in PD, we are unaware of previous studies giving estimates on its annual rate of progression over time. Regarding prior investigations of disease progression measured by the UPDRS motor score, one study found an annual increase of 0.7 units in outpatients aged 55 years at disease onset and followed for 6 years.[25] Other authors reported a 1.5% motor decline in patients with similar age at baseline and age at onset as in our cohort, but with a much shorter mean follow-up and

Table 4 *Baseline factors associated with greater disability during follow-up*

	Unified Parkinson Disease Rating Scale Activity of Daily Living score		Schwab and England scale	
Baseline variable	Difference in score	*p* Value	Difference in score	*p* Value
Age at onset	0.31	<0.001	−0.91	<0.001
Age*	0.56	<0.001	−1.44	<0.001
Disease duration	0.06	<0.001	−0.14	<0.001
Excessive daytime somnolence	3.92	0.005	−5.69	0.041
Mini-Mental State Examination	−0.34	0.027	1.28	<0.001
Montgomery and Aasberg Depression Rating Scale	0.24	0.021	NS	
Levodopa dose	NS		−0.01	0.026

* Derived from supplemental analysis.

disease duration.[26] We do not believe that these differences in observed progression rates between our study and previous studies are the result of insufficient medical treatment or occasional rating in off-state in our patients, although these are potential confounders. It is more likely that the differences are due to clinical and demographic differences between the respective study cohorts.

Our finding that age at onset interacted significantly with time, thus indicating a more rapid rate of motor progression in patients with older age at onset, may (at least in part) explain the differences between the rate of disease progression in our and previous studies. It is also in line with and confirms previous longitudinal investigations in which age at onset was found to be associated with a more rapid motor decline.[27-29] In other longitudinal studies, however, age at disease onset was not shown to independently predict the progression of motor impairment.[25,26] Interestingly, these studies were characterized by rather short follow-up or young patient cohorts.

Regarding the influence on motor decline, results have been inconsistent not only on the impact of age at onset, but also disease duration.[25-27,30,31] Although findings from a recent neuroimaging study and some clinical studies indicate that the rate of progression may decrease in a negative exponential manner with increasing symptom duration,[23,26] our study and other studies found no influence of disease duration on functional decline.[27,31] In this context, it is important to note that studies using imaging ligands to measure dopamine-metabolism or dopamine transporter activity, particularly those that include presymptomatic individuals, only reflect changes in dopaminergic transmitter systems. Likewise, results from short-term longitudinal studies of patients with short disease duration will mainly reflect disease progression due to pathology in dopaminergic pathways. Given that PD is a multisystem brain disorder in which symptoms with poor or no response to dopamine treatment become more frequent and severe later during disease duration, the clinically assessed disease progression is expected to be stable over time or even increased in later stages of the disease. This may explain why clinical long-term studies and those including patients with long disease duration measuring both dopaminergic and nondopaminergic symptoms, as it is done by the UPDRS, do not show any significant influence of disease duration on functional decline.

Our results may also indicate a different development of underlying neuropathologic changes depending on the patient's age at disease onset. Although it has recently been shown that the *LRRK2* mutation, which has also been found in Norwegian families, may account for clinically typical late-onset PD,[32,33] genetic factors seem to be more frequent and important in patients with younger age at disease onset.[34] In these patients with known gene mutations, the clinical presentation of parkinsonism is in some cases characterized by rather early development of motor problems, but generally a slower progression of motor symptoms and less development of nonmotor complications.[35] Our finding of a slower disease progression in patients with earlier disease onset may therefore indicate that at least a proportion of these patients has developed PD on a genetic basis, leading to less rapid motor progression, possibly due to slower and more restricted underlying changes in relevant areas of the brain.

Finally, due to collinearity, the influence of age could not be assessed in a model including both age at onset and disease duration. We therefore performed a supplemental analysis in which age was included instead of disease duration, with all other variables remaining unchanged. As expected in a disease that is not understood to primarily result from accelerated aging,[36] age at baseline did not predict more rapid functional decline. It was, however, associated with higher levels of motor impairment and disability during follow-up. This is in agreement with a recent cross-sectional study of 451 patients with PD, in which aging was found to contribute to the severity of motor signs, with most impact on axial symptoms like speech disturbance, gait problems, and postural instability.[37] Interestingly, also in neuropsychiatric symptoms such as cognitive impairment and dementia that are (like axial symptoms) thought to be due to underlying nondopaminergic changes outside the classic pathway of substantia nigra, advanced age rather than age at onset has been identified as an independent predictor.[15,38-42] A recent study of two large community-based cohorts of nondemented PD cases confirmed that older age at baseline, but not age at onset is an independent predictor of incident dementia in PD.[43] Moreover, results from a clinicopathological study of patients with PD and AD show intercorrelations between severities of neuronal loss in the locus coeruleus and nucleus basalis of Meynert, but not the substantia nigra.[44] These findings raise the question whether neurodegeneration underlying classic dopamine-responsive symptoms—like tremor, rigidity, and bradykinesia on one side and changes in nondopaminergic transmitter systems on the other—may be due to different pathologic mechanisms. As potential neuroprotective agents in PD should aim at dopaminergic as well as nondopaminergic systems, this issue should be clarified in future studies.

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