# Variable expression of Parkinson's disease:
## A base-line analysis of the DATATOP cohort

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**Article abstract**—The DATATOP database, which includes clinical information on 800 patients with early untreated Parkinson's disease (PD), is well suited to explore clinical heterogeneity in PD. Patients with early-onset PD (≤40 years, N = 33) reached the same level of disability as the late-onset PD (≥70 years, N = 85) group at a significantly slower rate (2.9 vs. 1.7 years). Early-onset PD patients functioned cognitively better than late-onset PD patients. Bradykinesia, and postural instability and gait difficulty (PIGD), were more common at onset in patients with a rapid rate of disease progression ("malignant PD"; duration of symptoms <1 year and Hoehn/Yahr stage of 2.5, N = 11) as compared with those with a relatively slow rate of progression ("benign PD"; duration of symptoms >4 years, N = 65). Comparisons of tremor-dominant PD (mean tremor score/mean PIGD score ≤1.5, N = 441) with the PIGD-dominant type (mean tremor score/mean PIGD score ≥1.0, N = 233) provided support for the existence of clinical subtypes. The PIGD group reported significantly greater subjective intellectual, motor, and occupational impairment than the tremor group. Stage II patients had higher depression scores than stage I patients. Among the patients participating in the DATATOP, older age at onset with bradykinesia, or with the PIGD form of PD, is associated with more functional disability than when the symptoms are dominated by tremor or begin at a younger age.

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The variability in clinical expression of Parkinson's disease (PD) suggests the existence of subgroups within PD with distinct clinical patterns and perhaps different pathogenic mechanisms. Alternatively, the clinical heterogeneity may merely reflect a broad spectrum of manifestations of 1 disease, characterized pathologically by the loss of pigmented neurons in the substantia nigra zona compacta, the presence of intracytoplasmic inclusions (Lewy bodies), and other pathologic changes.[1] Without a specific biologic marker or a test, the diagnosis of PD depends on clinical criteria. Attempts to define clinical subgroups may help delineate the diagnostic criteria and provide some insight into the question of whether PD is a unitary disease or a syndrome.[2] Several studies have addressed the question of clinical heterogeneity by proposing PD subgroups distinguished by age at onset, variable progression, family history of PD, patterns of motor symptoms, and by associated nonmotor findings such as dementia and depression.[3-19]

DATATOP (deprenyl and tocopherol antioxidative therapy of parkinsonism) is a multi-center trial designed to test the hypothesis that treatment with the antioxidative interventions, deprenyl and tocopherol, will slow the progression of the disease. The baseline database includes clinical information on 800 patients with early untreated PD.[20,21] Because these subjects are highly selected participants in a clinical trial, our study cannot reflect all PD patients. Nonetheless, this large and carefully studied group of untreated patients provides an important resource to study the clinical expression of PD. In this report, we describe characteristics of this group at study entry.

**Methods.** All 800 patients included in the DATATOP study had early PD with Hoehn/Yahr (H/Y) stage I or II,[4] were not receiving or requiring any anti-PD medications, and met stringent inclusion/exclusion criteria.[20] All were between 30 and 79 years old, and none had any evidence of dementia or severe (≥3 on a 0 to 4 scale) tremor. To explore the possibility that there are distinct clinical subtypes within PD, we defined 4 groups using demographic and clinical characteristics obtained at baseline evaluation. The criteria for the different groupings were defined before the data analysis and were based on previously reported possible subtypes[3-19] and on the collective clinical experience of the investigators. To the extent that these subtypes represent distinct clinical (and possibly pathologic) entities, the demographic and clinical variables that define the subtypes could have a predictive

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**Table 1. Early- vs. late-onset PD**

| Variable | Early onset (≤40 yrs) Mean | SD | N | Late onset (≥70 yrs) Mean | SD | N | p |
|---|---|---|---|---|---|---|---|
| Percent males | 63.6 | | 33 | 70.6 | | 85 | NS |
| Age at onset | 35.8 | 2.6 | 33 | 73.1 | 2.0 | 85 | 0.0001 |
| Age at entry | 38.7 | 3.1 | 33 | 74.8 | 2.1 | 85 | 0.0001 |
| Duration of symptoms | 2.9 | 1.6 | 33 | 1.7 | 1.0 | 85 | 0.0001 |
| H/Y stage at onset | 1.0 | 0.2 | 33 | 1.3 | 0.4 | 82 | 0.0001 |
| H/Y stage at entry | 1.5 | 0.5 | 33 | 1.7 | 0.5 | 85 | NS |
| S/E ADL score | 90.6 | 6.9 | 33 | 89.1 | 7.1 | 85 | NS |
| Mini-Mental score | 29.1 | 1.6 | 33 | 28.2 | 1.9 | 85 | 0.02 |
| Total recall* | 50.3 | 9.0 | 33 | 36.6 | 9.9 | 85 | 0.0001 |
| Sensory complaints | 0.8 | 1.0 | 33 | 0.4 | 0.6 | 85 | 0.03 |
| Tremor by history (L arm) | 1.0 | 1.1 | 33 | 0.5 | 0.8 | 85 | 0.03 |
| Rigidity (L arm) | 1.4 | 1.0 | 33 | 0.7 | 0.8 | 85 | 0.0004 |

* Late-onset patients also performed worse on a variety of neuropsychologic tests, including digit span, symbol digit modalities, long-term storage and recall, and Purdue pegboard.[20]

value concerning the associated symptoms, course, and prognosis.

*Early versus late onset.* In this comparison, the early-onset group was defined (a priori) as patients who according to the investigators had their 1st symptoms of PD at or before age 40 years. The late-onset group was arbitrarily defined as patients with onset of PD symptoms at or after age 70.

*Benign versus malignant status.* Patients in the benign group were defined by a duration of PD symptoms of at least 4 years before entry into the study. (Patients with duration greater than 5 years were excluded from DATATOP.) Despite the relatively long duration of symptoms, the disability of benign patients at entry was mild enough to satisfy the inclusion criteria of DATATOP. Patients included in the malignant group were defined as having PD symptoms for 1 year or less and progressing during this period of time (≤1 year) to a stage of 2.5 on the H/Y scale. (Patients with stage >2.5 were excluded from DATATOP.)

*H/Y stage I versus H/Y stage II.* The H/Y stage I group was defined as patients with H/Y stages 1.0 (unilateral involvement only) and 1.5 (unilateral and axial involvement). The H/Y stage II group was defined as patients with H/Y stages 2.0 (bilateral involvement without impairment of balance) and 2.5 (mild bilateral involvement with recovery on retropulsion by the pull test).

*Tremor versus PIGD types.* The Unified Parkinson's Disease Rating Scale (0 to 4 ratings, 0 = no or absent; 4 = most severe symptom or sign) was used to assess the severity of motor symptoms and signs.[22] An average global tremor score was calculated as the mean of the following 9 items: right and left arm tremor as determined by history, tremor at rest of either face, lips, or chin, all 4 limbs, and action or postural tremor in both arms as determined by the investigator's examination. A mean score for the complex of postural instability and gait difficulty (PIGD) was calculated as the mean of the following 5 items: falling, freezing, walking difficulty by history, and gait and postural instability by examination. The tremor group was defined as patients with a ratio of mean tremor score/mean PIGD score greater than or equal to 1.5; the PIGD group included all patients with a ratio of less than or equal to 1.0.

These 4 groups were compared with each other with respect to demographic and clinical variables including gender, age at onset, duration of symptoms, side of body 1st affected, initial symptom(s), H/Y stage, and Schwab and England Scale for Activities of Daily Living (S/E ADL) as determined retrospectively by the rater at onset, at diagnosis of PD, and at the time of study entry. Occupational disability, Mini-Mental score, Hamilton Depression Inventory, a comprehensive battery of neuropsychological tests, and all the items on the UPDRS[20,22] were rated prospectively. Chi-square tests of significance were performed for differences between the groups in nominal categorical variables (eg, gender, the presence or absence of certain initial symptoms, and family history). For continuous variables as well as ordinal categorical variables, 2-sample $t$ tests were used. Comparisons that yielded a nominal $p$ value $< 0.05$ were deemed significant. Because the analysis is merely exploratory, the reported results are not adjusted for multiple comparisons and, therefore, some of the "significant" results may be due to chance alone. After Bonferroni adjustment, $p$ values less than 0.0005 (0.05/100 comparisons) would be conservatively considered statistically significant.

To explore the possibility that the observed differences between the groups were due to age differences, we repeated the analyses adjusting for the covariate age. For continuous and ordinal categorical variables we adjusted for age using a simple analysis of covariance model, and for nominal categorical variables we used a logistic regression model. Spearman rank-order correlations were used to analyze relationships between variables.

**Results.** There were 800 patients included in the DATATOP: 530 men and 270 women, with age at onset of 59.0 ± 9.6 years (N = 748), duration of symptoms 2.1 ± 1.3 (N = 748), and age at randomization 61.1 ± 9.5 (N = 800).

*Early versus late onset.* Although at the time of randomization both early-onset (N = 33) and late-onset (N = 85) patients had similar degrees of disability as measured by H/Y stage and S/E ADL score, the early-onset group had a significantly longer estimated duration of symptoms (2.9 years) than the late-onset group (1.7 years), resulting in a slower progression of disease in the early-onset patients (table 1). This was also supported by the finding of a negative correlation between estimated duration of symptoms and age at onset; the younger age at onset was associated with a

**Table 2. Benign vs. malignant status**

| Variable | Benign (duration ≥4 yrs) Mean | SD | N | Malignant (duration ≤1 yr, H/Y stage = 2.5) Mean | SD | N | p |
|---|---|---|---|---|---|---|---|
| Percent males | 66.1 | | 65 | 72.7 | | 11 | NS |
| Age at onset | 55.4 | 9.6 | 65 | 68.2 | 3.9 | 11 | 0.0001 |
| Age at entry | 60.2 | 9.4 | 65 | 68.8 | 3.9 | 11 | 0.0001 |
| Duration of symptoms | 4.8 | 0.7 | 65 | 0.6 | 0.3 | 11 | 0.0001 |
| H/Y stage at entry | 1.8 | 0.5 | 65 | 2.5 | 0.0 | 11 | 0.0001 |
| Mini-Mental score* | 28.6 | 3.2 | 65 | 29.5 | 0.9 | 11 | 0.04 |
| Post. instab. | 0.3 | 0.5 | 65 | 1.0 | 0.2 | 11 | 0.0001 |
| At onset (%) | | | | | | | |
| Bradykinesia | 24.6 | | 65 | 54.5 | | 11 | 0.04 |
| Post. instab. | 7.7 | | 65 | 45.4 | | 11 | 0.0001 |

* NS when adjusted for age; NS differences in performance on any other neuropsychological tests.

longer estimated duration of symptoms (rho = −0.21, $p < 0.0001$). The early-onset patients also performed better than the late-onset patients on a variety of neuropsychological tests (table 1). Fifty-eight percent of the early-onset group had the left side of their body affected first, whereas only 32% of the late-onset patients had their 1st symptoms on the left side ($p < 0.05$). Patients with late-onset disease were more occupationally disabled at the time of entry into the study than the early-onset patients ($p < 0.0001$).

*Benign versus malignant status.* Patients with a benign course (N = 65) were compared with those who had a relatively malignant progression (N = 11) (table 2). The benign group had an onset earlier (age, 55.4 ± 9.6 years) than the malignant group (age, 68.2 ± 3.9 years). There was a significant difference between these groups in H/Y stage (1.8 vs. 2.5) as determined by the rater at the time of entry into the study. The average Mini-Mental State score was slightly worse in the malignant group, but the difference was not statistically significant when adjusted for age. All neuropsychological test scores and the motor subscores, except for increased postural instability of patients in the malignant group, were similar in the 2 groups at the time of entry into the study. Seventy-four percent of the benign group and 55% of the malignant group had tremor as the initial symptom. This difference was nearly significant when adjusted for age ($p = 0.06$). In contrast, bradykinesia (55% vs. 25%) and postural instability (45% vs. 8%) were more common at onset in patients who had more rapid estimated progression, even when adjusted for age.

*H/Y stage I versus stage II.* Patients with unilateral (with and without axial) symptoms, H/Y stage I (mean, 1.2 ± 0.24; N = 402) at the time of entry into DATATOP, were compared with those with bilateral symptoms, H/Y stage II (mean, 2.1 ± 0.21; N = 398) (table 3). Patients with bilateral findings had a significantly longer estimated duration of symptoms, older age at onset, lower S/E ADL scores, greater occupational disability, and higher Hamilton Depression Scores than the patients with predominantly unilateral symptoms. UPDRS subjective scores showed more intellectual impairment, depression, thought disorder, and lack of motivation in the stage II as compared with stage I patients. Stage II patients performed less well than the stage I patients on tests of total recall, long-term storage and recall, and short-term and delayed recall. However, since the stage II patients were older on average than the stage I patients, when the analysis of these cognitive variables was adjusted for age, these differences disappeared. Therefore, while age does not explain differences between the groups with regard to motor signs, it may explain many of the differences in cognitive signs. Stage II patients also had more difficulties with all activities of daily living as measured by the UPDRS. In addition, they scored worse in some motor functions including speech, facial expression, tremor at rest in the face and left side of the body, action/postural tremor in both arms, generalized rigidity, hand and leg agility, arising from a chair, gait, posture, postural stability, and bradykinesia. Stage I patients were more likely to have tremor at the onset of their symptoms, whereas bradykinesia, hypomimia, drooling, swallowing and speech problems, and PIGD were more likely to be present at onset in the stage II patients.

*Tremor versus PIGD types.* Patients with tremor-dominant PD (N = 233) were compared with those who had the PIGD-dominant type (N = 441) (table 4). The PIGD group had greater occupational disability and more intellectual impairment, depression, lack of motivation, and impairment in activities of daily living on UPDRS than the tremor group. However, there was no difference between this group and the tremor group in performance on formal neuropsychological tests. In addition to greater postural and gait difficulties, the PIGD patients had more severe body bradykinesia, difficulty rising from a chair, and poor posture. Rigidity was not different in the 2 groups at entry. However, rigidity, dystonia, gait, and postural difficulties were more likely to be present at the onset of the PIGD type of PD than in the tremor variety. The tremor-dominant patients not only had more severe tremor at rest, as expected, but also had more severe action-postural tremor, suggesting that this tremor is related to the typical resting tremor.

**Table 3. H/Y stage I vs. H/Y stage II**

| Variable | H/Y stage I (stage 1.0 or 1.5) Mean | SD | N | H/Y stage II (stage 2.0 or 2.5) Mean | SD | N | p |
|---|---|---|---|---|---|---|---|
| Percent males | 62.7 | | 402 | 69.8 | | 398 | 0.03 |
| Age at onset | 57.8 | 10.1 | 369 | 60.2 | 9.1 | 379 | 0.0004 |
| Age at entry | 59.8 | 9.9 | 402 | 62.5 | 8.9 | 398 | 0.0001 |
| Duration of symptoms | 2.0 | 1.1 | 369 | 2.3 | 1.3 | 379 | 0.0001 |
| H/Y stage at entry | 1.2 | 0.2 | 402 | 2.1 | 0.2 | 398 | 0.0001 |
| S/E ADL score | 93.0 | 6.3 | 402 | 88.8 | 7.9 | 398 | 0.0001 |
| Depression* | 2.4 | 2.8 | 401 | 3.0 | 3.0 | 398 | 0.005 |
| Occup. disabil. | 0.3 | 0.6 | 402 | 0.7 | 0.7 | 398 | 0.0001 |
| Purdue pegboard | 9.1 | 3.5 | 401 | 7.6 | 3.2 | 397 | 0.0001 |
| At onset (%) | | | | | | | |
| Tremor | 78.9 | | 402 | 71.4 | | 398 | 0.01 |
| Bradykinesia | 25.6 | | 402 | 35.2 | | 398 | 0.003 |
| Post. instab. | 6.0 | | 402 | 11.8 | | 398 | 0.004 |
| Gait problems | 9.5 | | 402 | 17.6 | | 398 | 0.001 |
| UPDRS score† | | | | | | | |

* Depression rated on the Hamilton scale.[20]
† Stage II patients performed worse on all UPDRS items except for sensory complaints and right arm tremor.

There was no statistically significant difference in reported family histories of PD (19.0% of 411 patients with known family history in the tremor group compared with 19.8% in the 222 patients in the PIGD group) between the 2 groups. Although the family history of essential tremor was reported twice as frequently in the tremor group (14.2% of 409 patients who knew their family history well enough to provide adequate information) as compared with the PIGD group (7.8% of 219 patients), this difference did not reach statistical significance. Family members were not systematically examined to verify the family histories.

Spearman correlation analyses show that PIGD correlates well with bradykinesia (rho = 0.52) and with S/E ADL (rho = −0.48; as PIGD increases S/E ADL worsens). In contrast, PIGD is not correlated with tremor (rho = 0.02).

**Discussion.** This analysis of baseline DATATOP database suggests that early-onset PD patients progress at a slower rate than late-onset patients. The study also provides support for the existence of at least 2 clinical subtypes of PD, the tremor-dominant and the PIGD forms. The data further indicates that patients with malignant PD have more PIGD and bradykinesia and less tremor at onset as compared with those with benign PD and that a deterioration in motor function is not necessarily accompanied by a cognitive decline.

While DATATOP provides a large and comprehensive database of clinical information in early PD, the results of this analysis must be interpreted cautiously. This is not an epidemiologic study and, therefore, the patients cannot be considered representative of the community as a whole. For example, because only patients between ages 30 and 79 are included in DATATOP, the late-onset group is not necessarily representative of all patients with onset of PD at old age. Furthermore, patients with a tremor score of 3 or more and patients with significant dementia and depression as measured by psychometric tests were excluded from DATATOP. Another potential pitfall in the interpretation of the data is that because of the large number of subjects, the power may be so great that very small, and perhaps clinically insignificant, differences are detected. Alternatively, since all the patients are in early stages of their disease, some may have not yet "differentiated" into 1 of the defined (eg, tremor-dominant or PIGD-dominant) categories. The analyses are also based on clinical data collected at a single point in time and, therefore, progression of disease can only be estimated. In order to correlate the rate of progression with clinical variables, we later intend to analyze prospectively collected data. The goal of the current study is to seek out consistent patterns in clinically related variables. Despite the stated caveats, several important qualitative conclusions have emerged from this exploratory analysis.

Although patients with late-onset PD were slightly more disabled at onset of their symptoms as measured by their H/Y stage than the early-onset patients, both groups had similar levels of disability at the time of entry into the study (table 1). However, late-onset patients appeared to reach this disability more rapidly than early-onset patients ($p < 0.0001$). While most studies also found that late-onset patients deteriorated more rapidly than those with early-onset disease,[3,4,9,12,14,18] some suggested that the 2 groups progressed at similar rates,[4,13] and 1 study concluded that early-onset patients actually progressed more rapidly.[3] Some,[11,12] but not all,[13] studies also noted that early-onset PD patients were more sensitive to levodopa than the late-onset patients and developed levodopa-induced dyskinesias and motor fluctuations earlier than did the late-onset patients. Our data also suggest that early-onset PD patients have better cognitive test scores than those with late-onset disease. However, this difference

**Table 4. Tremor vs. PIGD types**

| Variable* | Tremor (T/PIGD ≥ 1.5) Mean | SD | N | PIGD (T/PIGD ≤ 1.0) Mean | SD | N | p |
|---|---|---|---|---|---|---|---|
| Percent males | 69.4 | | 441 | 59.7 | | 233 | 0.01 |
| Age at onset | 59.0 | 9.6 | 414 | 58.9 | 9.7 | 218 | NS |
| Age at entry | 61.2 | 9.5 | 441 | 60.9 | 9.3 | 233 | NS |
| Duration of symptoms | 2.2 | 1.3 | 419 | 2.1 | 1.2 | 213 | NS |
| H/Y stage at entry | 1.6 | 0.5 | 441 | 1.8 | 0.5 | 233 | 0.0001 |
| S/E ADL score | 92.5 | 6.4 | 441 | 88.1 | 8.5 | 233 | 0.0001 |
| Occup. disabil. | 0.4 | 0.6 | 441 | 0.7 | 0.7 | 233 | 0.0001 |
| Intell. impair. | 0.3 | 0.5 | 441 | 0.4 | 0.5 | 233 | 0.01 |
| Lack of motivation | 0.4 | 0.6 | 441 | 0.5 | 0.6 | 233 | 0.009 |
| Speech diffic. | 0.5 | 0.6 | 441 | 0.7 | 0.7 | 233 | 0.0002 |
| Swallow. diffic. | 0.1 | 0.3 | 441 | 0.3 | 0.5 | 233 | 0.0001 |
| Falling | 0.0 | 0.2 | 441 | 0.1 | 0.4 | 233 | 0.0001 |
| Freezing | 0.0 | 0.1 | 441 | 0.2 | 0.4 | 233 | 0.0001 |
| Bradykinesia | 0.8 | 0.7 | 441 | 1.3 | 0.7 | 233 | 0.0001 |
| At onset (%) | | | | | | | |
| Tremor | 87.5 | | 441 | 47.6 | | 233 | 0.0001 |
| Bradykinesia | 24.0 | | 441 | 43.8 | | 233 | 0.0001 |
| Rigidity | 22.9 | | 441 | 37.3 | | 233 | 0.0001 |
| Post. instab. | 5.0 | | 441 | 15.0 | | 233 | 0.0001 |

* Tremor (rest and action) was worse in the tremor dominant group, whereas rapid succession movements, arising from chair, posture, gait, and postural stability were worse in the PIGD group; NS differences were found in age at onset, rigidity, performance on neuropsychological tests, or family history of tremor or PD.

may be explained by the younger age of the early-onset group at the time of entry into the study. Because the late-onset patients were more occupationally disabled than the early-onset group, even mild depression as a reaction to their motor disability may have adversely influenced their cognitive scores. Starkstein et al[19] noted that depression correlated with cognitive impairment and duration of symptoms in the early-onset PD group, whereas in the late-onset group, depression correlated more with impairments in activities of daily living.

While the differences between early- and late-onset subgroups have been interpreted as evidence for 2 distinct types of PD, it is possible that age alone, perhaps by contributing to a gradual loss of neuronal plasticity, may in some way alter the expression of an otherwise unitary disease. Similar interpretation could be applied to our finding that early-onset patients are more likely to have the benign form of PD than the patients with onset of symptoms later in life. However, the differences between benign and malignant groups persist even when the benign vs. malignant comparisons are adjusted for age. Therefore, even though the malignant group is older, the age difference cannot explain the clinical differences between the benign and malignant groups.

In 1 clinical-pathologic study of 57 parkinsonian and 49 control brains, the duration of parkinsonian symptoms correlated negatively with the age at onset.[23] However, use of tritiated alpha-dihydrotetrabenazine binding as an index of monoaminergic innervation of the caudate nucleus revealed no difference in the estimated rate of progression of striatal dopamine depletion between those patients who had onset of their symptoms after age 60 years (mean age at onset, 71.5 ± 1.4) and those with age at onset before age 60 (mean age at onset, 52.7 ± 1.2). The late-onset patients actually had higher density of binding and less severe striatal dopamine depletion at death than the early-onset patients, possibly because the late-onset patients did not live long enough for the pathologic process to fully develop.

Because each patient in the malignant PD group had, by definition, an H/Y stage of 2.5 as compared with a mean of 1.8 ± 0.4 for the benign group, it was not surprising that they had a greater degree of PIGD at the onset of PD symptoms (table 2). However, the lack of significant differences in cognitive performance between the 2 groups is an unexpected finding and it differs from most,[17,24-27] but not all,[28] previous studies which found a positive correlation between motor and intellectual impairment. Because DATATOP excluded patients with actual cognitive impairment, however, this finding cannot be easily compared to these other studies. Our analysis suggests that motor deterioration in PD does not inevitably parallel cognitive decline. Some studies, however, have found a correlation between cognitive impairment and gait disorder.[9,29] Because gait disorder in PD is usually unresponsive to levodopa, we postulate that cognitive impairment in PD results mostly from a nondopaminergic deficit. Degeneration of the nucleus basalis of Meynert and of the pedunculopontine nucleus, 2 cholinergic nuclei, occurs with normal aging but is more prominent in PD.[30] This may partly explain the cognitive decline seen particularly in elderly parkinsonian patients.[15,16] In addition, the cholinergic deficiency in these patients may partly correct the relative cholinergic preponderance, which is

typically expressed as parkinsonian tremor. Therefore, cognitive deficit may be inversely correlated with parkinsonian tremor.

The most compelling evidence for clinical subtypes in PD is provided by the analysis of tremor-dominant versus PIGD groups (table 4). The findings are in agreement with the report by Zetusky et al[9] and are consistent with our analysis of benign versus malignant types, suggesting that the PIGD type of PD has a less favorable outcome than the tremor-dominant PD. The criteria used to define the 2 categories seem to be quite sensitive and discriminating. Some of the 126 patients not included in the tremor or the PIGD group were probably in such early stages of their disease that they had not yet fully "differentiated" and, therefore, could not be accurately assigned to these categories. Although there was no difference in duration of symptoms, the PIGD group had a greater motor disability, suggesting a more aggressive course in this group as compared with the tremor group. However, there was no difference between the 2 groups in performance on neuropsychological tests, again suggesting relative independence of motor and cognitive changes in PD.

Our failure to detect differences in family history between the tremor and the PIGD groups may have been due to difficulty in obtaining an accurate history. The data on family histories were collected through an interview of the patients and their relatives, and the information was not verified by examinations of relatives. The 3.4% frequency of PD and 11% frequency of tremor among the 1st-degree relatives of our patients are much lower than the figures from other studies.[8,31,32]

We did not analyze our cohort for possible influence of gender on various clinical variables. However, in another study,[33] no differences were found between parkinsonian men and women with respect to age at onset, duration and progression of symptoms, and age at death.

Our study suggests that older age at onset and a presentation with PIGD and with bradykinesia are predictive of a more aggressive course than when the onset of PD symptoms is early and dominated by tremor. The validity of this will be tested with objective prospective follow-up in the same patients. Whether the tremor-dominant PD is biochemically, pathologically, and pathogenically different from the PIGD type must await a correlation between clinical characteristics and neurobiologic markers of underlying disease.

## References


1. Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:745-752.
2. Calne DB. Is "Parkinson's disease" one disease? J Neurol Neurosurg Psychiatry 1989;(Suppl):18-21.
3. Mjones H. Paralysis agitans: a clinical and genetic study. Acta Psychiatr Neurol Scand 1949;25(Suppl 54):1-195.
4. Hoehn MM, Yahr MD. Parkinsonism: onset, progression, and mortality. Neurology 1967;17:427-442.
5. Scott RM, Brody JA. Benign early onset of Parkinson's disease: a syndrome distinct from classical postencephalitic parkinsonism. Neurology 1971;21:366-368.
6. Birkmayer W, Reiderer P, Youdim JBH. Distinction between benign and malignant type of Parkinson's disease. Clin Neurol Neurosurg 1979;81:158-164.
7. Mortimer JA, Pirozzolo FJ, Hansch EC, Webster DD. Relationship of motor symptoms to intellectual deficits in Parkinson's disease. Neurology 1982;32:133-137.
8. Roy M, Boyer L, Barbeau A. A prospective study of 50 cases of familial Parkinson's disease. Can J Neurol Sci 1983;10:37-42.
9. Zetusky WJ, Jankovic J, Pirozzolo FJ. The heterogeneity of Parkinson's disease: clinical and prognostic implications. Neurology 1985;35:522-526.
10. Santamaria J, Tolosa E, Valles A. Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism. Neurology 1986;36:1130-1133.
11. Quinn N, Critchley P, Marsden CD. Young-onset Parkinson's disease. Mov Disord 1987;2:73-91.
12. Gershanik OS. Parkinsonism of early onset. In: Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders. Baltimore: Urban and Schwarzenberg, 1988:191-204.
13. Gibb WRG, Lees AJ. A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. Neurology 1988;38:1402-1406.
14. Goetz CG, Tanner CM, Stebbins GT, Buchman AS. Risk factors for progression in Parkinson's disease. Neurology 1988;38:1841-1844.
15. Hietanen M, Teravainen H. The effect of age of disease onset on neuropsychological performance in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:244-249.
16. Dubois B, Pillon B, Sternic N, Lhermitte F, Agid Y. Age-induced cognitive disturbances in Parkinson's disease. Neurology 1990;40:38-41.
17. Huber SJ, Paulson GW, Shuttleworth EC. Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988;51:855-858.
18. Diamond SG, Markham CH, Hoehn MM, et al. Effect of age at onset on progression and mortality in Parkinson's disease. Neurology 1989;39:1187-1190.
19. Starkstein SE, Berthier ML, Bolduc PL, et al. Depression in patients with early versus late onset of Parkinson's disease. Neurology 1989;39:1441-1445.
20. Parkinson Study Group. DATATOP: a multi-center controlled clinical trial in early Parkinson's disease. Arch Neurol 1989;46:1052-1060.
21. Parkinson Study Group. Deprenyl forestalls disability in early Parkinson's disease: a controlled clinical trial. N Engl J Med 1989;321:1364-1371.
22. Fahn S, Elton RL, UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, eds. Recent developments in Parkinson's disease, vol 2. Florham Park, NY: MacMillan Healthcare Information, 1987:153-163, 293-304.
23. Scherman D, Desnons C, Darchen F, et al. Striatal dopamine deficiency in Parkinson's disease: role of aging. Ann Neurol 1989;26:551-557.
24. Mayeux R, Stern Y, Rosen J, Leventhal J. Depression, intellectual impairment, and Parkinson's disease. Neurology 1981;31:645-650.
25. Mortimer JA, Pirozzolo FJ, Hansch EC, et al. Relationship of motor symptoms to intellectual deficits in Parkinson's disease. Neurology 1982;32:133-137.
26. Growdon JH, Corkin S, Desclos G, Rosen TJ. Hoehn and Yahr stages predict the extent of cognitive deficit in Parkinson's disease. Neurology 1987;37:157.
27. Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JAO, Mutch J. Clinical features predicting dementia in idiopathic Parkinson's disease: a follow-up study. Neurology 1990;40:1222-1224.
28. Mortimer JA, Jun SP, Kuskowski MA, Webster DD. Subtypes of Parkinson's disease defined by intellectual impairment. J Neural Transm 1987;24(Suppl):101-104.
29. Pillon B, Dubois B, Cusimano G, et al. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 1989;52:201-206.
30. Zweig RM, Jankel WR, Hedreen JC, et al. The pedunculopontine nucleus in Parkinson's disease. Ann Neurol 1989;26:41-46.
31. Jankovic J. Essential tremor and Parkinson's disease. Ann Neurol 1989;25:211.
32. Lang AE, Kierans C, Blair RDG. Family history of tremor in Parkinson's disease compared with those of controls and patients with idiopathic dystonia. Adv Neurol 1986;45:313-316.
33. Diamond SG, Markham CH, Hoehn MM, McDowell FH, Muenter MD. An examination of male-female differences in progression and mortality of Parkinson's disease. Neurology 1990;40:763-766.