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Effect of age and disease duration on parkinsonian motor scores under levodopa therapy

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Summary. One hundred and fifty patients suffering from Parkinson's disease were analysed for the expression of the motor symptoms during optimum response to levodopa therapy (subscale III of the Unified Parkinson's Disease Rating Scale). Patients were grouped according to age (≤64, 65–74, ≥75 years). Disease duration and daily levodopa dosage were similar in the three groups. Pooled residual scores for posture and gait impairment (PGI), tremor (T), rigidity (R) and distal motor impairment (DMI; hand and foot movements) increased with age (Kruskal-Wallis ANOVA). The parkinsonian scores were significantly higher than the scores of 150 age-matched normal controls (Mann-Whitney U test). The differences between the patients' scores and the scores of the age-matched controls increased with age. In spite of a significant increase in the daily levodopa dosage with disease duration (linear regression), PGI aggravated age-dependently, and DMI age-independently with symptom duration (Spearman rank correlation). In contrast, T and R did not increase with disease duration.

Keywords: Parkinson's disease, motor scores, age, disease duration, levodopa.

Introduction

Parkinson's disease without treatment leads to severe physical incapacity after 15 to 20 years of illness (Parkinson, 1817; Hoehn and Yahr, 1967). Levodopa therapy offers substantial relief from parkinsonian motor symptoms during the initial years of treatment. Long-term levodopa treatment, however, is complicated by abnormal involuntary movements, motor response fluctuations and aggravation of residual motor impairment (Barbeau, 1976; Marsden and Parkes, 1977; Maier Hoehn, 1983; Klawans, 1986; Bonnet et al., 1987; Parkinson's Disease Research Group in the U.K., 1993). Decreasing responsiveness to levodopa seems to affect parkinsonian motor symptoms differently (Klawans, 1986; Bonnet et al., 1987). Studies in patients with onset of the disease before the age of 65 years revealed a stable course of the

residual scores for tremor, rigidity, and rapid hand and foot movements during 10 to 20 years of levodopa therapy, whereas axial motor functions aggravated progressively (Klawans, 1986; Bonnet et al., 1987). Previous studies suggest decreasing responsiveness of parkinsonian motor symptoms to levodopa with advancing age (Blin et al., 1991; Durso et al., 1993). Therefore, the effect of disease duration on the expression of residual motor symptoms might be related to age. Motor functions decline, however, also with normal ageing, and age-associated non-parkinsonian pathologies, such as vascular encephalopathy or senile dementia of the Alzheimer type may mimick levodopa-resistant parkinsonian motor symptoms (Godwin-Austen et al., 1971; Parkes et al., 1974; McGeer et al., 1977; Newman et al., 1985; Morris et al., 1989). The aim of the study was to analyse the effect of age and disease duration on parkinsonian residual motor scores in patients with a wide range of age (31–91 years) and to quantify the effect of normal age-related decline in motor functions on residual motor scores under optimum levodopa therapy.

Subjects and methods

Patients

Between March 1991 and February 1992, 216 patients meeting the diagnostic criteria of Ward and Gibb for Parkinson's disease (Ward and Gibb, 1990) were seen in the in- and out-patients departments of our institution. Diagnosis was established by two clinicians experienced in the field of movement disorders (G.R. and M.W.). In one hundred and fifty patients the history was negative for cerebrovascular disorder, cerebral hypoxia, meningoencephalitis, epileptic seizures, abuse of alcohol or drugs, stereotactic treatment, antidopaminergic therapy, cerebral trauma with loss of consciousness for more than 30 minutes, and duration of symptoms was one year or longer. Cerebral CT (performed in 104 out of 150 included patients) was negative for cerebrovascular lesions, hydrocephalus, neoplasms and posttraumatic residuals. All patients responded markedly to dopaminergic therapy. They had been regularly followed up by the authors at 1 to 6 months intervals. Therapy was stable for a minimum duration of four weeks. In patients with clinical evidence of dementia (patients with severe dementia according to DSM III-R were not included) cognitive impairment had developed after the onset of parkinsonian motor symptoms (American Psychiatric Association, 1987). Patients with a history of disorientation, paranoid thinking and hallucinations were not included. Mini Mental State examination (Folstein et al., 1975) was performed in 108 (Table 1) and a neuropsychological screening of verbal intelligence, verbal and visual memory, visuospatial abilities and frontal lobe functions in 40 patients. Moreover, patients and their spouses were interviewed for impairment of orientation, memory, comprehension, mood, motivation, and social and occupational activities.

All patients were treated with levodopa combined with a peripheral decarboxylase inhibitor (levodopa:benserazide 4:1 N = 143; levodopa:carbidopa 10:1 N = 7) (Table 1). Levodopa slow-release preparations (levodopa-benserazide, Madopar CR) were given only at night. To reduce motor fluctuations, which could not be sufficiently overcome by modifications of levodopa therapy (increase of daily dosage and number of daily doses), 24 patients received bromocriptine. Three patients were given bromocriptine in combination with levodopa as initial treatment. Thirty-two patients were on L-deprenyl and 14 patients on anticholinergics. The therapeutic regimen was carefully modified until optimum therapeutic effect was achieved for the longest possible space of time of the waking day.

Table 1. Demographic and clinical data of the total group of patients and three age groups (≤64, 65–74, ≥75 years; Means ± S.D.)

	Total group N = 150	Age ≤ 64 N = 42	Age 65–74 N = 59	Age ≥75 N = 49	Kruskal-Wallis ANOVA H (p) values
Age	67.9 ± 10.9	*55.1 ± 7.6	69.4 ± 3.0***	78.5 ± 3.3***	136.2 (<.0001)
Male/female	68/82	25/17	26/33	17/32	
Age at disease onset○	59.8 ± 11.9	46.6 ± 8.7	61.1 ± 6.8***	70.7 ± 6.7***	95.3 (<.0001)
Disease duration○	8.1 ± 5.6	8.5 ± 5.4	8.4 ± 5.7	7.6 ± 5.6	1.4 (.506)
Duration levodopa therapy○	6.6 ± 6.6	7.7 ± 9.0	6.1 ± 4.9	5.6 ± 5.3	0.56 (.756)
Tremor□	1.6 ± 1.8	1.0 ± 1.2	1.7 ± 1.7*	2.2 ± 2.1	9.4 (.009)
Posture-gait impairment□	3.7 ± 2.6	1.9 ± 1.5	4.0 ± 2.5***	5.1 ± 2.7*	36.4 (<.0001)
Rigidity□	3.4 ± 2.5	2.5 ± 2.5	3.8 ± 2.7**	3.8 ± 2.2	8.9 (.012)
Distal motor impairment□	5.4 ± 2.5	4.3 ± 2.4	5.6 ± 2.4**	6.1 ± 2.3	11.4 (.003)
Global motor impairment□	17.5 ± 8.0	12.6 ± 6.7	18.6 ± 7.9***	21.2 ± 6.9	28.7 (<.0001)
Mod. Hoehn & Yahr score	2.6± 0.8	2.1 ± 0.8	2.8 ± 0.7**	2.9 ± 0.6	26.5 (<.0001)
Daily levodopa dosage (mg)	632 ± 303	714 ± 360	606 ± 275	578 ± 249	3.4 (.184)
Bromocriptine (mg)	16.8 ± 10.9 N = 27	19.1 ± 8.5 N = 12	20.1 ± 13.1 N = 9	8.0 ± 8.0 N = 6	5.0 (.084)
L-Deprenyl (mg)	9 ± 2.8 N = 32	10 ± 2.0 N = 14	8.3 ± 2.8 N = 11	9.2 ± 2.0 N = 7	2.7 (.260)
Cerebral CT	N = 104	N = 22	N = 43	N = 39	
Mini Mental State	27.3 ± 2.1	28.7 ± 0.8	26.9 ± 1.8***	26.3 ± 3.0	27.0 (<.0001)
Examination	N = 108	N = 32	N = 48	N = 28	
Intellectual impairment (UPDRS)	1.0 ± 0.6	0.9 ± 0.6	1.0 ± 0.6***	1.1 ± 0.6	26.1 (<.0001)
Thought disorder (UPDRS)	0.2 ± 0.4	0.1 ± 0.3	0.1 ± 0.3	0.3 ± 0.5*	6.8 (.034)

Mann-Whitney U test was used to compare patients aged 65–74 with patients aged ≤64 years (see column Age 65–74 years) and patients aged ≥75 years with those aged 65–74 years (see column Age ≥75 years). * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$; ○ years, □ see Subjects and Methods – Clinical Ratings

Clinical ratings

After the first or second morning dose of levodopa, the patients were observed until the therapeutic response was optimum. The severity of the parkinsonian motor symptoms was then estimated using subscale III (motor rating scale) and the modified Hoehn and Yahr scale of the Unified Parkinson's Disease Rating Scale (UPDRS, Fahn and Elton, 1987). To avoid ratings in states of diminished response to therapy, patients were asked if they considered the therapeutic response as optimum. Moreover, the scores were compared with former ratings during optimum "on". According to previously suggested groupings of parkinsonian motor symptoms (Barbeau and Pourcher, 1981; Poewe et al.,

1983; Bonnet et al., 1987; Jankovic et al., 1990), the following categories of motor symptoms were distinguished:

1) Tremor (T) score, calculated as the sum of the scores for tremor of the face and the mean scores of both sides for resting tremor of the upper and the lower extremities and action/postural tremor of the hands (range 0–16). 2) Score for posture and gait impairmant (PGI), sum of the residual scores for rising from a chair, posture, gait and postural stability (range 0–16). 3) Score for distal motor impairment (DMI), sum of the mean of the residual scores of both sides for tapping of the fingers, hand movements, rapid alternating movements of the hands and foot tapping (range 0–16). 4) Rigidity (R) score, resulting from the sum of the scores for rigidity in the neck and the means of rigidity in the upper and the lower extremities (range 0–12). The score for global motor impairment (GMI score, range 0–72) was calculated as the sum of the T, PGI, R and DMI scores plus the scores for speech, facial expression and body hypokinesia (Table 1). Demographic, clinical, diagnostic, therapeutic data of the patients and scores for intellectual impairment and thought disorder (UPDRS) are listed in Table 1.

Controls

To estimate motor impairment related to normal aging, 150 age-matched (±2 years), independant and mobile persons without history and clinical evidence of a neuropsychiatric disorder (spouses, siblings or other caregivers of patients) were rated for motor impairment by means of subscale III of the UPDRS (Table 2) (Fahn and Elton, 1987).

Statistics

The median age of the total group of patients was 70 years. Accordingly, three age groups of comparable size were distinguished (≤64 (31–64) years, N = 42; 65–74 years, N = 59; ≥75 (75–91) years, N = 49) which were compared for clinical parameters (Kruskal-Wallis ANOVA, H value corrected for ties; Mann-Whitney U test, U value corrected for ties). The clinical parameters of the patients were also compared with those of the controls (Mann-Whitney U test). To analyse the effect of age on the responsiveness of parkinsonian motor symptoms to treatment at variable disease duration, correlations were calculated in these age groups between the residual motor scores and disease

Table 2. Age and motor scores of 150 normal controls matched for age with the patients – total group and three age groups (≤64, 65–74, ≤75 years; Means ± S.D.)

	Total group N = 150	Age ≤64 N = 44	Age 65–74 N = 61	Age ≥75 N = 45	Kruskal-Wallis ANOVA H (p) values
Age	68.5 ± 10.4	55.5 ± 7.6	69.8 ± 2.7	79.4 ± 4.2	129.2 (<.0001)
Tremor	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.3	2.1 (.356)
Posture-gait impairment□	0.8 ± 1.1	0.3 ± 0.7	0.6 ± 0.8**	1.5 ± 1.4**	25.9 (<.0001)
Rigidity□	0.1 ± 0.4	0.1 ± 0.2	0.1 ± 0.5	0.2 ± 0.5	3.6 (.164)
Distal motor impairment□	1.8 ± 1.6	1.4 ± 1.4	1.6 ± 1.5*	2.4 ± 1.7*	9.8 (.0073)
Global motor impairment□	3.5 ± 3.0	2.4 ± 2.3	3.1 ± 2.8*	5.1 ± 3.3**	22.4 (<.0001)

Mann-Whitney U test was used to compare controls aged 65–74 with those aged ≤64 years (see column Age 65–74 years) and controls aged ≥75 years with the controls aged 65–74 years (see column Age ≥75 years). * $p \leq 0.05$, ** $p \leq 0.01$; □ see Subjects and Methods – Clinical Ratings

duration (Spearman rank-order correlation coefficient Rho corrected for ties). This approach was considered suitable since:

1) Age did not correlate with disease duration in either age group (≤64 years: Rho = 0.12, p = 0.423; ≥65–74 years: Rho = 0.09, p = 0.471; ≥75 years: Rho = 0.05, p = 0.721).

2) Factors contributing to response magnitude and, thus, expression of the residual motor symptoms, such as disease duration, duration of levodopa therapy and daily levodopa dosage (Horstink et al., 1990) were similar in the three age groups (Table 1, Mann-Whitney U test) as was the correlation between daily levodopa dosage (y) and disease duration (x) (Linear regression; ≤64 years: $y = 25.8x + 483$, $R = 0.41$, $p = 0.006$; 65–74 years: $y = 22.5x + 449$, $R = 0.40$, $p = 0.003$; ≥75 years: $y = 21.9x + 406$, $R = 0.44$, $p = 0.002$).

3) Bromocriptine was given at low to intermediate dosages which, according to previous studies, have little effect on the amplitude of the motor response (Larsen et al., 1984). The differences in the treatment between the groups were not significant (Table 1). Moreover, daily dosage of bromocriptine did not correlate with disease duration in either age group (Spearman rank-order correlation; ≤64 years: Rho = 0.18, p = 0.238; 65–74 years: Rho = 0.12, p = 0.342; ≥75 years: Rho = 0.21, p = 0.150). Nevertheless, the statistics (comparisons between the age groups and correlations between residual scores and disease duration) were calculated separately for the patients without bromocriptine therapy. The proportion of patients taking L-deprenyl decreased with age. However, the differences in L-deprenyl treatment between the three age groups were not significant (Table 1) and daily dosage did not correlate with disease duration in either age group (Rho = 0.05, −0.43, −0.62; p = 0.865, 0.131, 0.130, respectively).

Results

Age and age at disease onset were significantly different in the three age groups (Table 1). All assessed residual motor scores and the modified Hoehn and Yahr score were significantly lower in patients aged under 65 years than in the two other age groups. In the group aged 75 and over, the PGI score was significantly higher than in patients aged 65–74 years. The remaining residual scores of these two groups were not significantly different (Kruskal Wallis ANOVA, Mann-Whitney U test).

The age of the patients was not different from that of the controls (U = 0.36, p = 0.722, Mann-Whitney U test). In the group of controls, the scores for PGI, DMI and GMI increased with advancing age. T and R did not vary with age (Kruskal-Wallis ANOVA, Mann-Whitney U test, Table 2). All motor scores of the controls were significantly lower than the residual scores of the patients ($U \geq 6.35$, $p < 0.0001$, Mann-Whitney U test). The differences between the scores of the patients and those of the controls increased with age (Tables 1, 2).

In the total group of patients, residual GMI (Rho = 0.25, p = 0.003) and the scores for PGI (Rho = 0.24, p = 0.003) and DMI (Rho = 0.29, p = 0.0004) correlated with disease duration, whereas no correlation of T and R with disease duration was found (Rho = 0.03 and 0.04; p = 0.715 and 0.611, respectively; Spearman rank correlation) (Fig. 1).

In patients aged under 65 years, the residual motor scores for T (Rho = 0.08, p = 0.615) and R (Rho = −0.12, p = 0.424) did not correlate with disease duration. GMI tended to correlate positively with symptom duration (Rho = 0.27, p = 0.086). Significant positive correlations of PGI (Rho = 0.33, p = 0.036) and DMI (Rho = 0.32, p = 0.039) with disease duration were found (Fig. 1).

In patients aged 65–74 years, the residual scores for T and R did not correlate with symptom duration (Rho = −0.04 and 0.04; p = 0.752 and 0.769, respectively). There was a significant increase in GMI (Rho = 0.26, p = 0.048), PGI (Rho = 0.27, p = 0.043) and DMI (Rho = 0.31, p = 0.018) with disease duration (Fig. 1).

In patients aged 75 and over, T did not correlate with disease duration (Rho = 0.05, p = 0.728). A trend to an aggravation of R with duration of the motor symptoms was found (Rho = 0.25, p = 0.087). GMI (Rho = 0.43, p = 0.003) as well as PGI (Rho = 0.42, p = 0.004) and DMI (Rho = 0.31, p = 0.037) correlated positively with disease duration (Fig. 1).

All motor scores of the controls were lower than the intercepts of the linear regression between residual motor scores and disease duration in the patients' groups (corresponding to residual motor impairment at disease onset) (Table 2, Fig. 1). After omission of the patients on bromocriptine a trend to a correlation between PGI and disease duration (Rho = 1.83, p = 0.067) and no correlation of disease duration with DMI (Rho = 1.5, p = 0.139) were found in the age group under 65 years. The remaining correlations were similar to those obtained when patients on bromocriptine were included (results not shown). No statistical differences in the residual scores and the correlations of disease duration with residual scores were found between male and female patients (results not shown).

Discussion

The study is cross sectional. To avoid inhomogeneities in the patients' selection, all parkinsonian patients seen during a period of one year were considered for inclusion in the study (admission to our institution not regulated by age, social status, severity of the disease, etc.). The demographic and clinical data of the patients were homogenous and in accordance with other studies (Maier Hoehn, 1983; Klawans, 1986; Bonnet et al., 1987; Diamond et al., 1989; Blin et al., 1991). Sample distortion may also occur in longitudinal studies in elderly subjects (e.g. loss to follow-up, concomitant diseases, deaths) (Maier Hoehn, 1983). To minimize variations in the estimation of the residual motor scores, most clinical ratings were performed by one clinician (G.R.). The motor scores were carefully assessed and pooled according to previously suggested groupings (scores for T, R, PGI, DMI and GMI) (Barbeau and Pourcher, 1981; Poewe et al., 1983; Jankovic et al., 1990). Nevertheless, the findings of the present study should be interpreted with caution.

We did not evaluate the patients after levodopa withdrawal for several reasons: firstly, a substantial proportion of patients, mostly persons with advanced Parkinson's disease, did not consent to therapy withdrawal. Secondly, ceiling effects of the rating scales may bias ratings of advanced parkinsonian motor symptoms, leading to an underestimation of severe motor symptoms (Bonnet et al., 1987). Thirdly, after withdrawal from levodopa motor functions may fluctuate so that it may be difficult to assess baseline motor scores (Nutt et al., 1988).

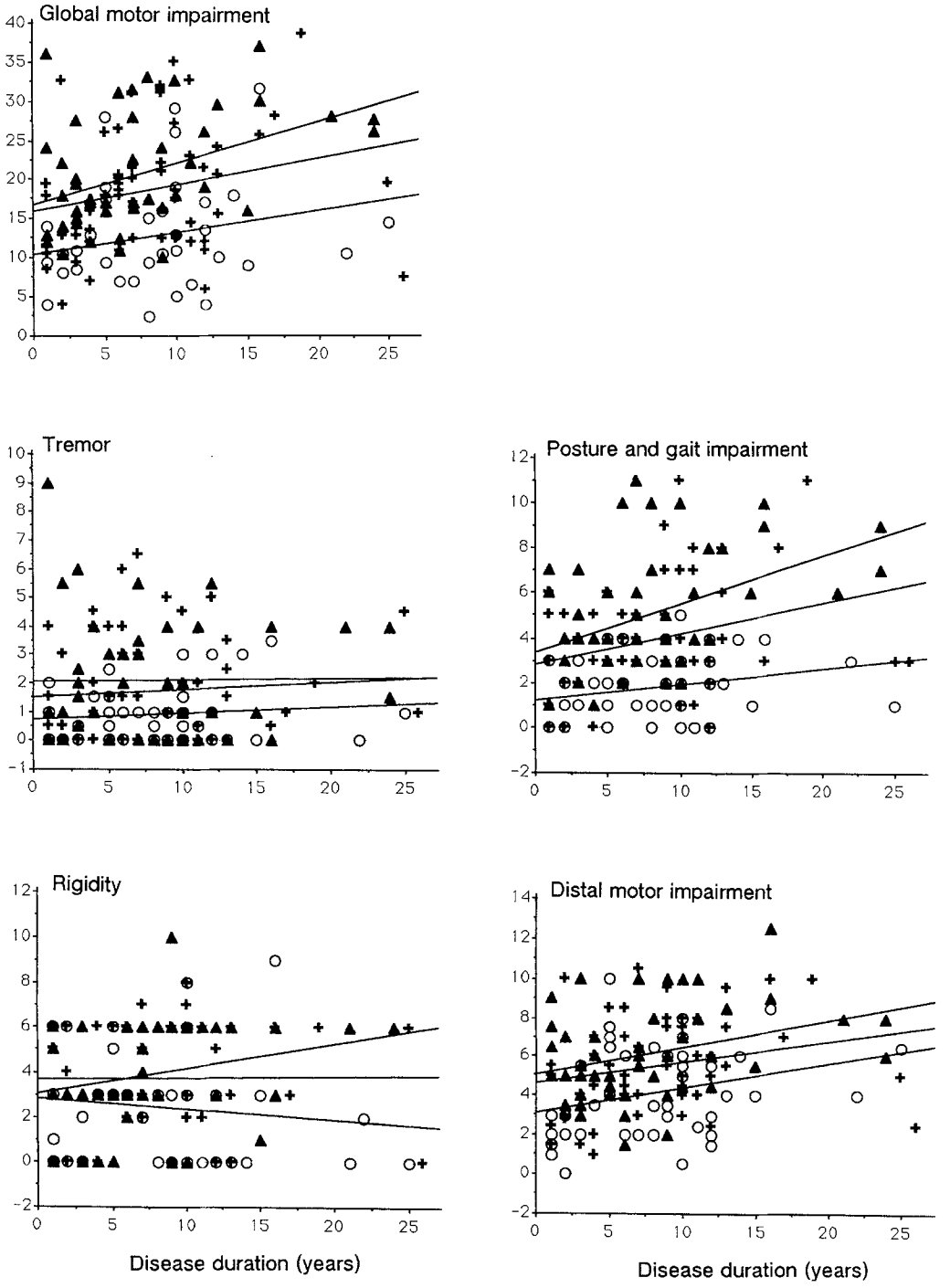

Fig. 1. Residual motor scores of the three groups of patients plotted against disease duration. Circles: Patients aged ≤64 years. Crosses: Patients aged 65–74 years. Triangles: Patients aged ≥75 years. Upper regression lines: patients ≥75 years; middle lines: patients 65–74 years; lower lines: patients ≤64 years. Statistical evaluation see Results (Spearman rank-order correlation)

In agreement with previous studies, the residual motor scores increased with age and age at disease onset (Table 1) (Godwin-Austen et al., 1971; Danielczyk et al., 1980; Goetz et al., 1988; Blin et al., 1991; Durso et al., 1993). This finding is also in accordance with a study demonstration an age-related increase in global parkinsonian disability (Diamond et al., 1989). The smaller differences in the residual scores between the groups aged 65–74 and ≥75 compared to the patients aged ≤64 and 65–74 years might result from smaller age differences between the two former compared to the two latter groups. The dosages of levodopa were statistically similar in the three age groups. The somewhat albeit insignificantly higher dosages of levodopa in patients aged under 65 years (Table 1) might have contributed to the lower residual scores in this group. However, they did not influence the correlations between disease duration and residual scores in the young age group. The increasing proportion of female patients with advancing age is consistant with previous studies (Mendel, 1911). Differences in the male/female ratio, however, did not contribute to the age-related differences in the residual scores and correlations between disease duration and residual scores.

In summarizing, our study in patients without clinical evidence of non-parkinsonian pathology corroborates in part previous studies demonstrating an aggravation of residual motor impairment with age and a differential course of residual motor symptoms with advancing disease duration (stable course of T and R, progression of axial motor symptoms; Godwin-Austen et al., 1971; Klawans, 1986; Bonnet et al., 1987; Goetz et al., 1988). In addition, the study shows, that the increase in the parkinsonian residual motor scores with age exceeds the deterioration of motor performance with age in normal controls.

How could the partial unresponsiveness of parkinsonian motor symptoms to dopaminergic therapy and the differences in the residual motor scores between the three age groups be interpreted?

The magnitude of the motor response to levodopa is thought to be determined by 1) the cerebral availability of the medication, 2) the sensitivity of dopamine receptors, and 3) the severity of dopaminergic and non-dopaminergic lesions (Nutt et al., 1987; Kempster et al., 1989; Durso et al., 1989; Horstink et al., 1990).

1) Systemic availability of levodopa was probably not different in the three groups. Daily levodopa dosage was similar and pharmacokinetics of levodopa have been shown not to deteriorate with age (Evans et al., 1980). The differences in L-deprenyl and bromocriptine treatment between the age groups were not significant so that the increase in the residual scores with age were probably not significantly related to the treatment with these substances (Table 1). 2) Duration of the disease and levodopa treatment, factors thought to determine the magnitude of a dopaminergic motor response, were similar in the three age groups (Nutt et al., 1987; Kempster et al., 1989; Durso et al., 1989; Horstink et al., 1990). 3) Age-related non-parkinsonian lesions, such as vascular encephalopathy or dementia of the Alzheimer type, may mimick Parkinson's disease and are in general unresponsive to dopaminergic therapy. However, concomitant cerebral disorders were, to the best of our knowledge, ruled out.

The mechanisms contributing to the differential increase in thus parkinsonian residual scores with advancing age and disease duration are unclear and cannot be explained by our study. Availability of endogenous dopamine and dopamine receptor density decline with increasing age (Marksman et al., 1979; Coté and Kremzner, 1983; De Keyser et al., 1990; Martin et al., 1989) and the combined age- and disease-related changes in the dopaminergic neurotransmission might insufficiently be compensated by dopaminergic therapy (Lloyd and Hornykiewicz, 1970; Lloyd et al., 1975; Melamed et al., 1981; Leenders et al., 1986; Hornykiewicz and Kish, 1986; Ahlskog et al., 1991; Brooks et al., 1992).

The differences in the aggravation of the residual motor scores with advancing disease duration could be related to different scaling of the motor symptoms in the UPDRS. Abnormal involuntary movements, more frequently observed in younger than in older patients, could also aggravate axial and distal motor functions (Gibb and Lees, 1988). Since the loss of dopaminergic substantia nigra neurons is probably not related to age and decelerates with the disease duration (Riederer and Wuketich, 1976; Scherman et al., 1989; Fearnley and Lees, 1991), the aggravation of PGI and DMI with disease duration and the rather stable course T and R could be related to symptom-specific differences in the pattern of mesencephalic dopaminergic cell and striatal dopamine loss in Parkinson's disease (Kish et al., 1988; Hirsch et al., 1992; Jellinger and Paulus, 1992). Moreover, non-dopaminergic lesions have been hypothesised to underly the progression of axial motor symptoms in Parkinson's disease (Lakke, 1985; Hirsch et al., 1987; Jellinger, 1988; Koller et al., 1989; Halliday et al., 1990).

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