Segmental progression of early untreated Parkinson's disease: a novel approach to clinical rating

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ABSTRACT

Objective: To assess the ability of potentially neuroprotective compounds to slow the progression of Parkinson's disease (PD), sensitive rating scales are needed to detect clinically meaningful effects. The topographical progression of motor signs in early untreated PD was evaluated to complement current clinical ratings and enhance the sensitivity to detect disease progression.

Methods: 12 patients referred for diagnostic evaluation of untreated de novo PD underwent detailed clinical assessment of motor parkinsonian signs at baseline and after 6 and 12 months of follow-up using the Unified Parkinson's Disease Rating Scale, motor part (UPDRS-III), and a newly developed approach of detailed segmental rating taking into account the localisation of motor signs in all of the major joints and muscle groups in the body. The progression of PD, as measured with the UPDRS-III, was compared with the segmental ratings.

Results: UPDRS-III scores and segmental ratings for rigidity and rest and postural tremor, but not bradykinesia, progressed significantly during the observation period. Progression of normalised segmental ratings for rigidity and tremor was significantly larger than the UPDRS-III ratings over 1 year. The segmental ratings for rigidity and tremor as well as their combination with the UPDRS-III bradykinesia rating were more sensitive a measure for progression of PD than the UPDRS-III.

Conclusions: Taking into account the segmental evolution of parkinsonian signs may be a useful adjunct to UPDRS-III evaluations to measure clinical disease progression of PD. If validated in subsequent larger cohorts, this may be useful in trials of neuroprotective agents.

The largest unmet need in the current treatment of Parkinson's disease (PD) is a neuroprotective compound that can slow or even halt disease progression. Basic research has identified a wide array of potentially neuroprotective molecules that are effective in in vitro and in animal models of PD, but the clinical testing of such molecules is a formidable challenge because of the hundreds of (de novo) patients required for such trials and the need for lengthy follow-up periods.[1] The idea of performing exploratory neuroprotection trials to screen for effective compounds, which may then be tested in larger patient cohorts over prolonged periods of time,[2] is attractive but requires more sensitive tools to assess neuroprotection than those currently available. A more discriminating method for assessing the clinical status of the patients would be helpful in this respect.

Degeneration of dopaminergic neurons in the substantia nigra pars compacta in PD follows a specific spatiotemporal gradient along the rostral, medial and dorsal axes.[3 4] The nigrostriatal neurons along these axes project to specific regions of the striatum where the body parts—legs (dorsolateral putamen), face (ventromedial putamen) and arms (in between the two aforementioned areas)—are selectively represented.[5] Therefore, the body parts clinically affected would be expected to evolve following an individual spatial gradient along the body over time. This was tested in one retrospective study[6] but no prospective study has been conducted to date in which the somatotopic progression of signs was evaluated.

The Unified Parkinson's Disease Rating Scale, part III (UPDRS-III),[7] the scale most widely used to assess the severity of PD motor signs, has been used as a primary outcome measure in trials assessing neuroprotection. The UPDRS-III provides a good overall estimate of disease severity, most particularly akinesia and bradykinesia.[8] Whereas distal and more proximal bradykinesia is differentially assessed with the UPDRS-III, tremor and rigidity are rated for each limb as a whole, not taking into account the segmental progression along each arm or leg. The consequence is that identical UPDRS-III scores may be obtained for a severe focal deficit and a widely distributed but mild impairment.

In this study, we prospectively analysed the anatomical progression of signs in de novo PD patients, over a period of 12 months, with a newly designed clinical rating approach that evaluates the cardinal PD signs in all the major joints and muscle groups in the body. In this pilot, proof of concept approach, we suggest that including the segmental progression of tremor and rigidity in the clinical rating of parkinsonian signs may improve the sensitivity of the assessment of disease progression.

PATIENT AND METHODS

Patients

Twelve de novo PD patients, seven men and five women, who did not require immediate dopaminergic treatment, were prospectively recruited in our outpatient clinic over a period of 14 months. All fulfilled established diagnostic criteria for PD,[9] except for their response to levodopa, which was not assessed. After evaluation of their state at inclusion (month 0), patients were again assessed after 7.5 (1.7) months (M6) and 13.6 (2.6) months (M12). Two patients could not be examined at the intermediate time point. Ten patients had rest tremor at inclusion, the remaining two had a predominantly akineto-rigid form of PD initially but developed mild rest tremor during the study period.

Clinical assessment

History and examination

At inclusion (M0), patients were interviewed for information on their medical and surgical history, exposure to toxins, current and past medication, family history of neurological disorders, educational level, socioprofessional status and neurological signs (with special emphasis on sleep disorders, hyposmia and dysautonomia), and a detailed history of parkinsonian signs and symptoms (with special emphasis on evolution and modulating factors). Weight, height and vital signs were recorded, and a complete medical and neurological examination was performed by the same examiner throughout the study.

Classical rating scales

At each visit (M0, M6 and M12), patients were examined with the UPDRS parts I–III,[7] as well as the Hoehn and Yahr[10] and the Schwab and England scales.[11]

Segmental evaluation of signs

The severity of rigidity was rated, with the patient supine and maximally relaxed, on a scale ranging from 0 to 5: 0, no rigidity; 1, no rigidity at rest but rigidity when the contralateral arm was lifted (Froment's sign)[12]; 2, minimal rigidity, detected by slight pressure on the joint, present at rest; 3, slight rigidity, detected easily by the examiner but passive movement is not limited and rigidity is overcome with very little effort; 4, moderate rigidity that requires some effort to overcome but passive movement is not limited; and 5, pronounced rigidity that requires clear effort to overcome and passive movement is limited (equivalent to UPDRS rating 3). Rigidity was assessed in the neck by flexion/extension and rotation, in the trunk by rotation of the patient's shoulders either standing or seated, in the left and right shoulder by both rotation and elevation, in the left and right elbow by flexion/extension and pronation/supination rated separately, in the left and right wrist, hip (rotation), knee and ankle. Rating of rigidity required 5–10 min. The sum of the ratings provided a rigidity severity score (R-sev). The number of locations where the rigidity score was not 0 provided a topographical rigidity score (R-top).

The severity of rest tremor (maximal amplitude observed during the examination) was assessed on the face/lips, head/neck, fingers, hands, forearms, upper arms, thighs, calves and feet, on a 5 point scale, both relaxed and during a mental effort (repeatedly subtracting 7 from 100; naming the last five French presidents backwards): 0, absent; 1, minimal (amplitude <0.5 cm—ie, barely visible); 2, slight (amplitude <1 cm—ie, visible but discrete); 3, moderate (amplitude >1 cm); 4, severe (amplitude ⩾5 cm). As rest tremor in the relaxed state varied greatly as a function of the patient's psychological tension during the examination, which was videotaped, only the ratings during a mental effort were analysed.

Postural tremor, assessed proximally and distally in all four limbs, and action tremor, also assessed on all four limbs, was scored in the same way as rest tremor. Rating of tremor required 5–10 min. A tremor severity score (T-sev) and a topographical tremor score (T-top) were assigned for rest, postural and action tremor, individually, as described for rigidity.

Akinesia was assessed by repetitive tapping tasks at the following locations bilaterally: all fingers, with the forearm and hand fixed to a surface to limit wrist movement; wrists, with the forearm fixed on a surface; legs, stepping up and down on a 43 cm high stool; feet, tapping with the sole while the heel rests on the ground, tapping alternately with the heel and the toes,

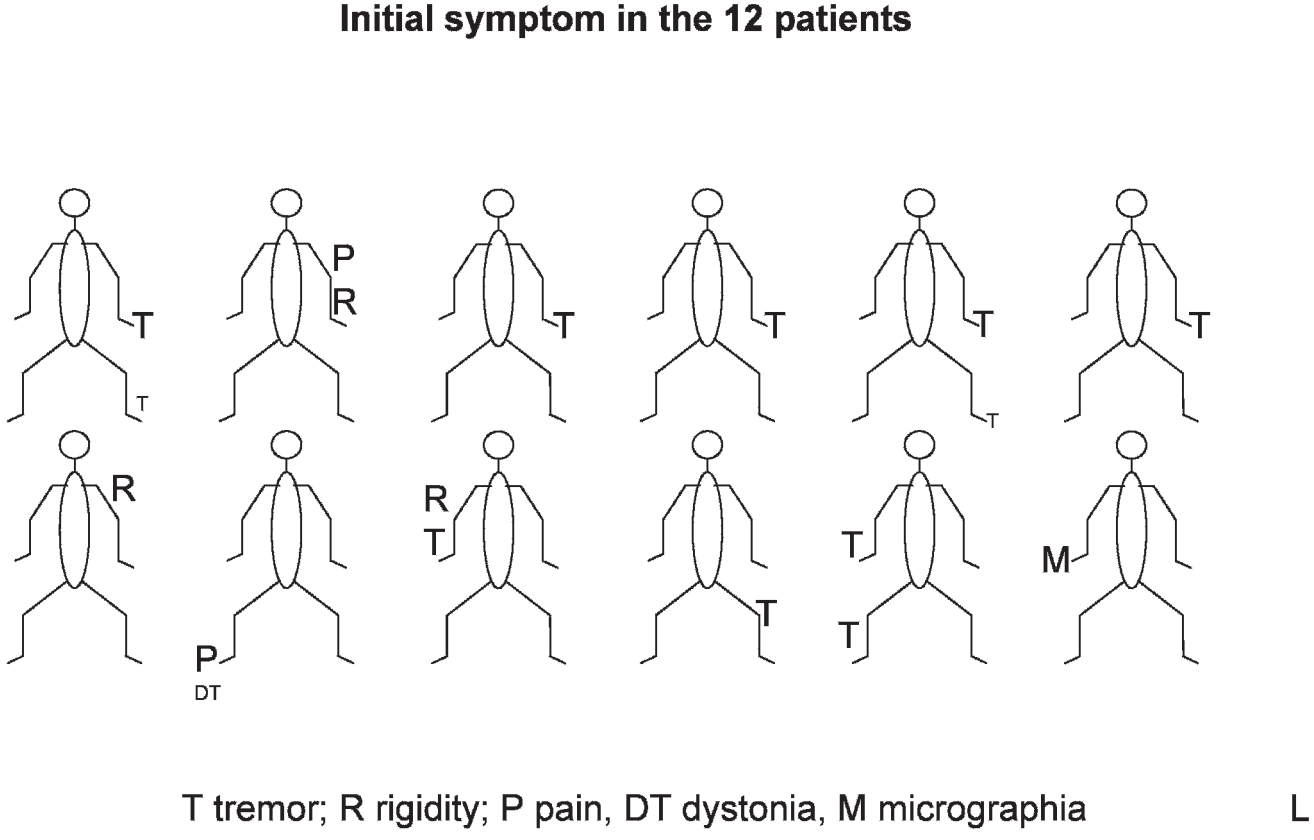

Figure 1 Initial symptoms of Parkinson's disease in the 12 patients studied.

and tapping with the big toe with the foot fixed on a surface. The number of taps per joint recorded over a 30 s period was the outcome measure for each segmental bradykinesia test. A tapping test according to the CAPSIT was performed for each arm over a period of 60 s.[13] Patients were asked to move as quickly as possible. The experimental setting included a mechanical counter for the repetitive movements.

Composite scores

A composite tremor and rigidity severity (c-sev) score combined the severity scores for rigidity and rest tremor. A total severity score included the c-sev score and the UPDRS-III bradykinesia ratings (items 23–26, and item 31). A composite topographical tremor and rigidity (c-top) score for rigidity and rest tremor combined the localisation scores for rigidity and tremor. These scores were constructed post hoc.

Statistical analysis

The main outcome measures were the c-sev score, the c-top score and the total severity score. All outcome measures were analysed with repeated measures ANOVA to assess progression over time. If the ANOVA yielded a significant result for a given measure, a Tukey test was performed to assess progression during the first (M0–M6) and second half (M6–M12) of the observation period. A p value of $\leqslant 0.05$ was considered significant. However, as multiple tests were performed to explore the segmental progression of bradykinesia, a p value of $\leqslant 0.002$ was considered significant for the measures of bradykinesia.

To compare our new scores with the UPDRS-III in terms of sensitivity for progression, three pairwise comparisons were performed between each of the three new scores (c-sev, c-top and total severity score) and the UPDRS-III. For each comparison, three statistical approaches were used. (1) A repeated measures ANOVA was conducted on the raw data for assessing the interaction between the assessment number (M0, M6, M12) and the scale chosen (UPDRS-III or one of the new scales)—that is, the lack of parallelism between the score curves. As the patients served as their own controls, a paired design was chosen. (2) The ratings were normalised by calculating a z score (subtraction of the mean at M0, then division by the SD at M0); then progression as measured with the different scales has been compared by comparing the distributions of differences between M0 and M6 and M0 and M12 using Wilcoxon's signed rank test. (3) The ratings were normalised with respect to baseline defined as 100%; then the relative increments were compared using paired Wilcoxon

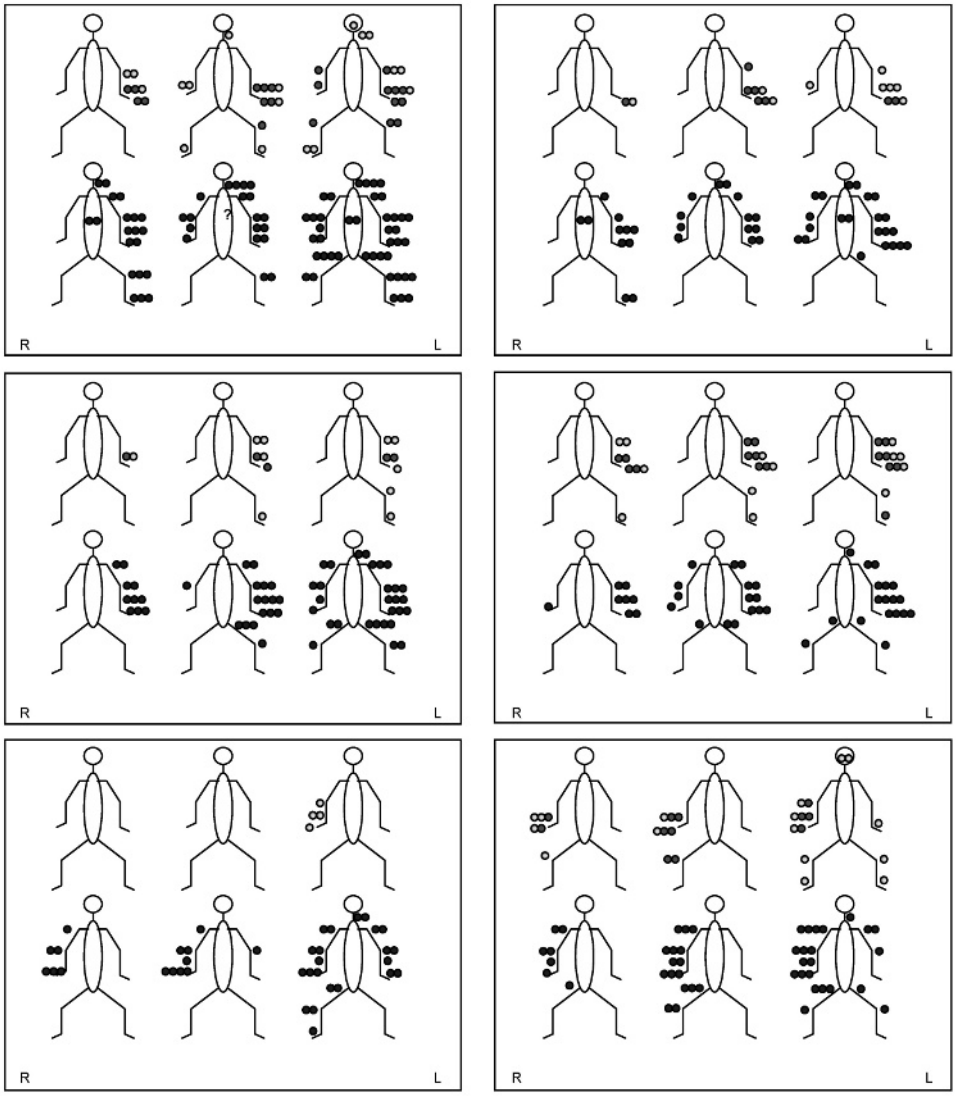

Figure 2 Illustration of the topographical progression of rest tremor and rigidity in six exemplary patients. The data of one patient are grouped in one box. The upper row within a box refers to rest tremor (dark grey/light grey); the lower row within a box refers to rigidity (black). Within one box, progression is illustrated from M0 (left) over M6 (middle) to M12 (right). Symptom severity is indicated by the number of dots according to the 6 point rating scale. Dark grey dots indicate rest tremor under relaxed condition; light grey dots indicate worsening of rest tremor during a mental task. L, left; R, right.

Table 1 Hoehn and Yahr stage, scores on the Schwab and England and UPDRS-II and III scales, as well as the subscores on the UPDRS-III (tremor, rigidity and bradykinesia score) at baseline and after 6 and 12 months

	Baseline	6 months	12 months	p Value
UPDRS-I	0.67 (0.98) (0–3)	1.40 (1.43) (0–4)	1.50 (1.24) (0–4)	NS
UPDRS-II	3.58 (2.47) (1–8)	6.70 (1.89) (4–9)	11.58 (5.04) (5–22)	0.0001†
UPDRS-III	13.42 (5.93) (8–30)	18.70 (6.52) (10–30)	24.25 (7.03) (14–39)	1.9×10^{-7}*†
Axial score	0.83 (1.19) (0–4)	1.50 (1.18) (0–4)	1.50 (1.31) (0–4)	NS
Tremor score	2.50 (1.78) (0–5)	3.40 (2.27) (0–7)	5.08 (2.15) (2–8)	0.0001†
Rigidity score	3.33 (1.97) (1–8)	4.50 (1.35) (3–7)	6.75 (2.18) (3–10)	2.3×10^{-7}*†
Bradykinesia score	6.17 (3.01) (2–13)	8.50 (5.44) (1–16)	9.5 (4.27) (2–17)	0.006
Hoehn and Yahr	1.50 (0.60) (1–2.5)	1.95 (0.50) (1–2.5)	2.00 (0) (2–2)	0.03
Schwab and England (%)	92.5 (4.52) (90–100)	89.0 (3.2) (80–90)	88.3 (3.9) (80–90)	0.04
Resting tremor				
Severity score (T-sev)	4.33 (3.34) (0–11)	7.10 (4.53) (0–13)	9.25 (5.00) (1–19)	0.001
Localisation score (T-top)	2.08 (1.31) (0–4)	3.40 (2.17) (0–7)	5.25 (2.53) (1–10)	0.0001†
Member score	1.17 (0.72) (0–2)	1.70 (1.42) (0–5)	2.67 (1.37) (1–5)	0.0004†
Postural tremor				
Severity score	0.58 (0.90) (0–2)	1.80 (1.62) (0–5)	2.75 (1.71) (1–6)	0.004
Member score	0.42 (0.67) (0–2)	0.80 (0.42) (0–1)	1.25 (0.62) (1–3)	0.04
Action tremor				
Severity score	0.42 (0.67) (0–2)	0.70 (0.48) (0–1)	0.58 (0.67) (0–2)	NS
Member score	0.42 (0.67) (0–2)	0.70 (0.48) (0–1)	0.50 (0.52) (0–1)	NS
Rigidity				
Severity score (R-sev)	10.83 (6.03) (4–20)	15.80 (4.59) (9–24)	27.00 (11.45) (14–51)	0.0001†
Localisation score (R-top)	5.58 (2.19) (3–9)	8.10 (1.97) (5–11)	12.08 (2.35) (9–15)	0.007*†
Member score	2.25 (0.97) (1–4)	3.30 (0.95) (2–5)	4.42 (0.67) (3–5)	2×10^{-6}*†
Bradykinesia				
Finger tapping right digit I	79 (24) (56–127)	96 (22) (72–148)	76 (22) (39–102)	NS
Finger tapping right digit II	105 (35) (67–189)	101 (19) (74–137)	102 (54) (30–254)	NS
Finger tapping right digit III	102 (38) (52–185)	105 (26) (78–163)	94 (32) (21–148)	NS
Finger tapping right digit IV	81 (25) (40–121)	87 (24) (48–137)	90 (33) (31–148)	NS
Finger tapping right digit V	73 (12) (56–90)	77 (17) (54–112)	78 (25) (31–128)	NS
Finger tapping left digit I	80 (23) (38–115)	72 (20) (48–110)	69 (16) (34–91)	NS
Finger tapping left digit II	87 (14) (62–110)	87 (25) (58–137)	89 (22) (54–129)	NS
Finger tapping left digit III	84 (22) (52–126)	86 (23) (54–127)	87 (22) (56–139)	NS
Finger tapping left digit IV	77 (31) (28–126)	75 (24) (50–125)	73 (17) (52–116)	NS
Finger tapping left digit V	72 (21) (44–120)	63 (20) (42–106)	69 (22) (36–124)	NS
Tapping right wrist	105 (24) (83–149)	108 (20) (83–146)	91 (29) (37–133)	NS
Tapping left wrist	91 (22) (64–124)	91 (28) (62–157)	83 (27) (54–156)	NS
Tapping right arm	115 (25) (82–158)	112 (25) (74–149)	105 (26) (69–139)	NS
Tapping left arm	102 (21) (63–145)	97 (23) (54–148)	93 (21) (50–140)	NS
Tapping right proximal leg	30 (4) (24–40)	33 (6) (26–46)	32 (6) (23–45)	NS
Tapping left proximal leg	28 (6) (20–39)	31 (6) (22–42)	30 (6) (20–41)	NS
Tapping right heel/toes	38 (8) (26–52)	40 (11) (24–57)	40 (11) (24–66)	NS
Tapping left heel/toes	37 (10) (26–60)	36 (12) (24–62)	35 (12) (24–68)	NS
Tapping right foot	77 (20) (47–110)	95 (28) (68–160)	91 (25) (60–153)	NS
Tapping left foot	74 (15) (54–95)	86 (21) (54–113)	77 (25) (30–110)	NS
Tapping right toe I	76 (12) (53–92)	78 (17) (42–100)	78 (23) (41–126)	NS
Tapping left toe I	68 (18) (42–93)	64 (26) (29–111)	57 (24) (27–102)	NS
Composite tremor and rigidity severity score (c-sev)	15.17 (7.42) (6–30)	22.90 (6.77) (9–33)	36.25 (13.61) (22–63)	1.3×10^{-7}*†
Composite tremor and rigidity localisation score (c-top)	7.67 (2.39) (3–11)	11.50 (3.27) (5–17)	17.33 (3.23) (14–25)	6.5×10^{-9}*†
Total severity score	21.33 (9.24) (12–40)	31.40 (7.73) (24–45)	45.75 (15.19) (32–78)	3.3×10^{-8}*†

Values are mean (SD) (range).
*Tukey $p<0.05$ for comparison of 6 months versus baseline.
†Tukey $p<0.05$ for comparison of 12 months versus 6 months.
R-sev, rigidity severity score; R-top, topographical rigidity score; T-sev, tremor severity score; T-top, topographical tremor score; UPDRS, Unified Parkinson's Disease Rating Scale.

signed rank sum tests. A p value of $\leqslant 0.05$ was considered significant and all the tests were two sided. Computations were performed using the SAS V.8 statistical package.

Inter-rater agreement was assessed for tremor using videotapes of the assessments. The raters were blinded to all previous ratings given. The inter-rater correlation coefficient κ (kappa) was calculated as described elsewhere.[14] For inter-rater agreement with identical ratings, κ was 0.50. For inter-rater agreement ± 1 point, κ was 0.91.

RESULTS

Mean age at first symptom was 52.2 (8.0) years, and mean age at inclusion was 53.9 (7.8) years, with a mean of 20.9 (15.7) months since the very first putative clinical manifestation of PD. Parkinsonian signs began on the left side in eight patients and on the right side in four. Ten patients were right-handed; two were left-handed and trained at school to be ambidextrous. The initial signs or symptoms of each patient are shown in fig 1. No patient reported exposure to toxins. Family

history for rest tremor and parkinsonism was negative in all patients for first and second degree relatives.

Rigidity was initially found in the upper extremities in half of the patients and in the upper and lower extremities in the other half; at M12, all of the patients had rigidity in the upper and lower extremities. It was bilateral in only four patients at M0, but in 11 at M12. Rest tremor was initially observed in the upper and lower extremities of four patients, in the upper extremity only in five and in the lower extremity only in one. Two patients did not have tremor initially. Rest tremor spread to the upper and lower limbs in nine patients but remained restricted to the upper extremities in three. It was unilateral at M0 in all 10 patients who had tremor initially and became bilateral in six by M12. The two patients who had no tremor initially developed unilateral rest tremor by M12.

Rigidity often progressed faster than tremor. None of the patients developed bilateral tremor before bilateral rigidity and four developed bilateral tremor and rigidity simultaneously. Only one patient had unilateral rigidity and tremor for the 12 month period of the study. The segmental evolution of the signs in individual patients is illustrated in fig 2.

During the course of the study, the Hoehn and Yahr stage, scores on the Schwab and England and UPDRS-II and III scales, as well as the subscores on the UPDRS-III (tremor, rigidity and bradykinesia score) worsened significantly (table 1). Segmental rigidity, rest and postural tremor scores also worsened from M0 to M12 (table 1). The UPDRS-I, UPDRS-III axial score and the segmental action tremor and bradykinesia scores did not change significantly during the study period (table 1). As the segmental bradykinesia ratings were insensitive to change over time and because we wanted to include the aspects of bradykinesia in a global score, the UPDRS-III bradykinesia score was used (rather than the segmental bradykinesia ratings) to build the total severity score.

According to the UPDRS-III evaluation, parkinsonian signs progressed 192 (47)% (from 13.42 (5.93) to 24.25 (7.03)) between M0 and M12, but 259 (75)% when the c-sev score was used, 248 (95)% when the c-top score was used and 227 (52)% when the total severity score was used (fig 3). The slope of progression of the UPDRS-III score was less steep than the slope of progression of the c-sev score ($p = 0.0022$) and the total severity score ($p = 0.0001$) but not the c-top score. However, all three composite scores were more sensitive than the UPDRS-III to detect clinical progression of PD defined as the normalised difference of follow-up ratings compared with baseline after 12 months (p values are given for normalisation with a z score and for normalisation with percentage, respectively: for the c-sev score, $p = 0.02/0.005$; for the c-top score, $p = 0.001/0.02$; for the total severity score, $p = 0.03/0.02$). After 6 months, there was no significant difference in terms of detection of progression of PD between the UPDRS-III and the composite scores.

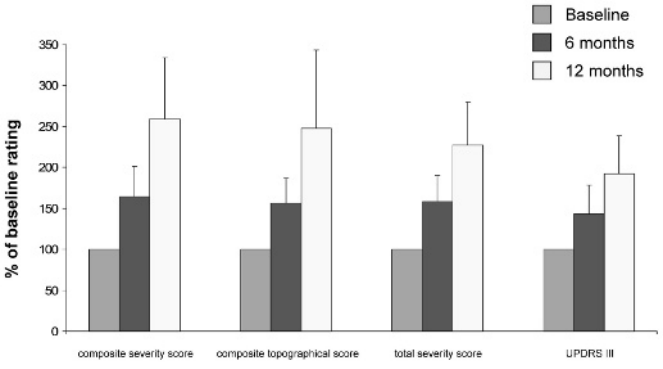

Figure 3 Progression of clinical signs of Parkinson's disease as assessed with the three composite scores and the Unified Parkinson's Disease Rating Scale, motor part (UPDRS-III). Baseline values are set at 100%.

DISCUSSION

This pilot study demonstrates that a segmental examination of tremor and rigidity in de novo PD patients, combined with the bradykinesia scores from the UPDRS III, is more sensitive for detecting changes in disease severity over 1 year than the UPDRS-III.

In our study, rigidity evolved faster but in a similar distribution pattern as tremor. This may be due to the fact that rigidity is more easily detected than tremor or maybe just more apparent on examination. Increasing rigidity may mask rest tremor.[15] A recent multi-tracer positron emission tomographic study of patients with monosymptomatic resting tremor compared with early PD patients displaying all three cardinal signs suggested that rigidity and tremor correlated with a presynaptic dopaminergic deficit along an anteroposterior putaminal gradient.[16] This supports our observation that the segmental evolution of rigidity and tremor is similar and reflects a common nigrostriatal dopaminergic deficiency, at least in early disease stages.

Akinesia/bradykinesia scores obtained in the segmental repetitive movement tests unexpectedly did not change over the 12 month study period, in contrast with the UPDRS-III items that assess akinesia/bradykinesia. The difficulty inherent in the tests may be responsible in that they required the active cooperation of the patient. Indeed, the voluntary effort most of our patients made during these quantitative tapping tests—to prove to themselves that PD had not measurably progressed—might have compensated for potentially worsened motor impairments, especially at this early stage of the disease. Quantification of the UPDRS bradykinesia ratings is not obvious for the patients during the examination and there may have been less incentive to outperform the baseline rating than in the tapping tasks where performance is quantified on a counter visible to the patient during the effort. It was previously suggested that attention can compensate to some degree for the basal ganglia deficit responsible for akinesia/bradykinesia.[17] However, these authors also proposed that the engagement of compensatory processes may lead to reduced performance in other tasks which would become apparent when running two tasks simultaneously.[17] In accordance with this, we observed in many patients an increase in tremor in the limbs not involved in tapping during these tasks. Thus we do not exclude the fact that akinesia/bradykinesia can be unmasked and possibly amplified in a segmental evaluation (compared with UPDRS-III items) if a further simultaneous task were added. Although we applied established diagnostic criteria for PD, the age of onset in our patients was relatively young, and levodopa response could not be evaluated in all patients. However, the aim of this pilot study was to clinically assess parkinsonian signs and not to ascertain a diagnosis of PD.

In conclusion, we believe that our segmental rating approach will usefully complement the UPDRS-III akinesia/bradykinesia section and increase the sensitivity of clinical evaluations. The goal of this preliminary pilot study was to provide a proof of concept. Although the detection of clinical progression was significantly enhanced using a segmental tremor and rigidity

rating, even in a small group of patients, further validation of the new scores in a larger cohort is needed. Yet, within small exploratory neuroprotection trials where one investigator studies all patients, this method may be a worthwhile adjunct to UPDRS-III testing in the foreseeable future.

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REFERENCES

1. **Clarke CE.** Neuroprotection and pharmacotherapy for motor symptoms in Parkinson's disease. *Lancet Neurol* 2004;**3**:466–74.
2. **Choi DW.** Exploratory clinical testing of neuroscience drugs. *Nat Neurosci* 2002;**5**(Suppl):1023–5.
3. **Damier P,** Hirsch EC, Agid Y, *et al*. The substantia nigra of the human brain. I. Nigrosomes and the nigral matrix, a compartmental organization based on calbindin D(28K) immunohistochemistry. *Brain* 1999;**122**:1421–36.
4. **Damier P,** Hirsch EC, Agid Y, *et al*. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. *Brain* 1999;**122**:1437–48.
5. **Brown LL,** Sharp FR. Metabolic mapping of rat striatum: somatotopic organization of sensorimotor activity. *Brain Res* 1995;**686**:207–22.
6. **Dickson JM,** Grunewald RA. Somatic symptom progression in idiopathic Parkinson's disease. *Parkinsonism Relat Disord* 2004;**10**:487–92.
7. **Fahn S,** Elton RL, UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, eds. *Recent developments in Parkinson's disease*, *vol 2*. Florham Park, NY: MacMillan Healthcare Information, 1987:153–63.
8. **Ramaker C,** Marinus J, Stiggelbout AM, *et al*. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord* 2002;**17**:867–76.
9. **Hughes AJ,** Daniel SE, Ben-Shlomo Y, *et al*. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002;**125**:861–70.
10. **Hoehn MM,** Yahr MD. Parkinsonism onset, progression and mortality. *Neurology* 1967;**17**:427–42.
11. **Schwab JF,** England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson ML, eds. *Third symposium on Parkinson's disease*. Edinburgh: E&S Livingstone Ltd, 1969:152–7.
12. **Broussolle E,** Krack P, Thobois S, *et al*. Contribution of Jules Froment to the study of parkinsonian rigidity. *Mov Disord* 2007;**22**:909–14.
13. **Defer GL,** Widner H, Marié RM, *et al*. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;**14**:572–84.
14. **Altman DG.** *Practical statistics for medial research*. London: Chapman and Hall/CRC, 1999:403–9.
15. **Winogrodzka A,** Wagenaar RC, Bergmans P, *et al*. Rigidity decreases resting tremor intensity in Parkinson's disease: A [(123)I]beta-CIT SPECT study in early, nonmedicated patients. *Mov Disord* 2001;**16**:1033–40.
16. **Ghaemi M,** Raethjen J, Hilker R, *et al*. Monosymptomatic resting tremor and Parkinson's disease: a multitracer positron emission tomographic study. *Mov Disord* 2002;**17**:782–8.
17. **Berardelli A,** Rothwell JC, Thompson PD, *et al*. Pathophysiology of bradykinesia in Parkinson's disease. *Brain* 2001;**124**:2131–46.