How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder

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Parkinsonism, as a gradually progressive disorder, has a prodromal interval during which neurodegeneration has begun but cardinal manifestations have not fully developed. A systematic direct assessment of this interval has never been performed. Since patients with idiopathic REM sleep behaviour disorder are at very high risk of parkinsonism, they provide a unique opportunity to observe directly the development of parkinsonism. Patients with idiopathic REM sleep behaviour disorder in an ongoing cohort study were evaluated annually with several quantitative motor measures, including the Unified Parkinson’s Disease Rating Scale, Purdue Pegboard, alternate-tap test and timed up-and-go. Patients who developed parkinsonism were identified from this cohort and matched according to age to normal controls. Their results on motor testing from the preceding years were plotted, and then assessed with regression analysis, to determine when markers first deviated from normal values. Sensitivity and specificity of quantitative motor tests for diagnosing prodromal parkinsonism were assessed. Of 78 patients, 20 developed parkinsonism. On regression analysis, the Unified Parkinson’s Disease Rating Scale first intersected normal values at an estimated 4.5 years before diagnosis. Voice and face akinesia intersected earliest (estimated prodromal interval = 9.8 years), followed by rigidity (4.4 years), gait abnormalities (4.4 years) and limb bradykinesia (4.2 years). Quantitative motor tests intersected normal values at longer prodromal intervals than subjective examination (Purdue Pegboard = 8.6 years, alternate-tap = 8.2, timed up-and-go = 6.3). Using Purdue Pegboard and the alternate-tap test, parkinsonism could be detected with 71–82% sensitivity and specificity 3 years before diagnosis, whereas a Unified Parkinson’s Disease Rating Scale score >4 identified prodromal parkinsonism with 88% sensitivity and 94% specificity 2 years before diagnosis. Removal of action tremor scores improved sensitivity to 94% and specificity to 97% at 2 years before diagnosis (cut-off >3). Although distinction between conditions was often difficult, prodromal dementia with Lewy bodies appeared to have a slower progression than Parkinson’s disease (prodromal interval = 6.0 versus 3.8 years). Using a cut-off of Unified Parkinson’s Disease Rating Scale >3 (excluding action tremor), 25% of patients with ‘still-idiopathic’ REM sleep behaviour disorder
demonstrated evidence of possible prodromal parkinsonism. Therefore, using direct assessment of motor examination before parkinsonism in a REM sleep behaviour disorder, we have estimated a prodromal interval of ~4.5 years on the Unified Parkinson’s Disease Rating Scale; other quantitative markers may detect parkinsonism earlier. Simple quantitative motor measures may be capable of reliably detecting parkinsonism, even before a clinical diagnosis can be made by experienced movement disorders neurologists.

Keywords: Parkinson’s disease; REM sleep behaviour disorders
Abbreviations: AUC = area under the curve; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction

Parkinsonism is a gradually progressive disorder, implying that there is a period during which the disease has started, but definitive symptoms or motor signs sufficient to permit a diagnosis have not yet appeared. It has been estimated that clinical symptoms of parkinsonism develop after 70–80% of striatal dopamine is depleted, corresponding to 30–50% cell death of dopaminergic neurons (Fearnley and Lees, 1991; Stoessl, 2007).

Numerous studies have tried to identify the duration and characteristics of the ‘pre-motor’ (here termed ‘prodromal’) interval of Parkinson’s disease. Methodology in these studies generally centres on measurement of the slope of a marker in patients who have already been diagnosed with parkinsonism, then back-extrapolating to estimate the time at which the measure crosses normal control values. Dopaminergic functional imaging studies using this approach have estimated a duration of prodromal parkinsonism averaging 3–15 years (estimates vary considerably according to the type of imaging marker and patient-related factors such as age) (Fearnley and Lees, 1991; Vingerhoets et al., 1994; Morrish et al., 1998; Fuente-Fernandez et al., 2011). Assessment of whole brain glucose utilization network patterns has estimated a prodromal interval of 4.5 years (Moeller and Eidelberg, 1997).

Extrapolation based upon progression of the Unified Parkinson’s Disease Rating Scale (UPDRS) in early disease suggests an interval of ~5 years (Poewe and Mahlknecht, 2009). Neuropathological studies based on neuronal cell counts have estimated an onset of cell loss in the substantia nigra pars compacta ~5 years before diagnosis (Fearnley and Lees, 1991). Since patients in these studies already have parkinsonism, all of these estimates are limited by the need to rely upon extensive back-extrapolation. Systematic direct measurement of prodromal parkinsonism has not been performed.

Idiopathic REM sleep behaviour disorder is characterized by loss of the normal atonia of REM sleep, such that patients apparently act out the content of their dreams. Longitudinal studies estimate that >50% of patients with idiopathic REM sleep behaviour disorder will develop neurodegenerative parkinsonism (almost exclusively Parkinson’s disease, multiple system atrophy or dementia with Lewy bodies) with a mean latency from REM sleep behaviour disorder onset to disease diagnosis of 13 years (Schenck et al., 1996; Iranzo et al., 2006; Postuma et al., 2009a). This high conversion rate to neurodegenerative disease provides a unique opportunity to observe directly the development of clinical parkinsonism.

Since 2004, we have been following a cohort of patients with idiopathic REM sleep behaviour disorder, to assess risk of neurodegenerative disease and to measure markers and predictors of neurodegeneration. Patients are evaluated annually with a battery of tests, including the UPDRS and other simple quantitative motor tests. This assessment of motor measures in patients initially free of parkinsonism allows the prospective assessment of motor changes before and during development of clinically defined parkinsonism.

In this study, we examined the progression of motor signs before diagnosis of disease, focusing on several questions:

(i) When do patients destined to develop parkinsonism begin to deviate from normal values on simple quantitative motor measures (i.e. when does motor parkinsonism ‘start’)?
(ii) Do the different cardinal manifestations of parkinsonism (i.e. bradykinesia, rigidity, tremor or gait dysfunction) or the different locations of motor abnormalities (i.e. bulbar, limbs, gait) present at different times in prodromal parkinsonism? In other words, which features ‘start’ first?
(iii) Which quantitative motor measures are most sensitive and specific in detecting parkinsonism at diagnosis and in prodromal stages? How soon before formal diagnosis of parkinsonism can motor changes be identified with good sensitivity/specificity?
(iv) Are there differences in progression of parkinsonism in patients diagnosed with Parkinson’s disease or dementia with Lewy bodies?

Patients and methods

Patients

Patients with idiopathic REM sleep behaviour disorder were diagnosed according to International Classification of Sleep Disorders-II criteria, as REM sleep without atonia by polysomnography and history or videographic evidence of dream enactment (American Academy of Sleep Medicine, 2007; Montplaisir et al., 2010). Patients gave written informed consent and ethics approval was obtained from the Sacré-Coeur ethics board. For inclusion, all patients had to be free of parkinsonism and dementia at enrolment and had a complete baseline examination including quantitative motor markers. Details of inclusion and exclusion criteria have been published elsewhere (Postuma et al., 2009b).

Patients were then followed annually and at each visit, a systematic motor assessment was performed. To enhance future clinical
application of the study, all motor measures were selected to be assessable in a clinical office setting. These measures included:

(i) UPDRS: total UPDRS (1987 version; Fahn et al., 1987) was measured, and scores were divided according to location and cardinal manifestation. Cardinal manifestations were classified as akinesia/bradykinesia (items 18, 19, 23–27 and 31), rigidity (item 22a–e), rest tremor (item 20a–e) and gait disorder (items 28–31). Locations were defined as voice/face (items 18 and 19), limb (items 20–26) and gait/body bradykinesia (items 28–31).

(ii) Alternate-tap test: a test of motor speed in the hands (Nutt et al., 2000). Subjects were given 1 min to alternately tap two 2.5-cm diameter metal discs attached to a manual counter, mounted 20 cm apart. The total number of taps at the end of 1 min was the outcome measure.

(iii) Purdue Pegboard: a test of hand dexterity, motor speed and finger–eye coordination (Desrosiers et al., 1995). Subjects were given 30 s to transfer a series of pins from a dish into corresponding holes. This was performed separately in each hand, and the average number of pins placed was the outcome measure.

(iv) Timed up-and-go test: a measure of gait and transfer speed (Podsiadlo and Richardson, 1991). Subjects were instructed to rise quickly from a chair, walk 3 m, turn and return to sit in the same chair. Two trials were performed and the average of these two trials was the outcome measure.

At each visit, a systematic assessment for parkinsonism was performed by a movement disorders specialist (R.P.). Parkinsonism was defined according to UK Brain Bank criteria as the presence of bradykinesia in association with one of rest tremor, rigidity or postural instability (Hughes et al., 1992). The presence of dementia was also assessed with a standardized neuropsychological battery (Gagnon et al., 2009) and the Movement Disorders Society Criteria for Parkinson’s disease dementia (Dubois et al., 2007). We matched our patients to a group of normal controls according to age (at Year 0 assessment) in a 2:1 proportion of controls to cases. Controls were examined with the same measures as patients, at a single time point. Also, for comparison, we analysed the same motor measures in patients with idiopathic REM sleep behaviour disorder who, as of their last visit, did not have parkinsonism (i.e. ‘still-idiopathic’ REM sleep behaviour disorder).

**Analysis**

For each patient who developed parkinsonism, the year of diagnosis was set at Year 0. Motor measures in each of the previous years were then plotted backwards in time, assessing these measures before parkinsonism was diagnosed (Year −1, Year −2, etc.). If motor measures were missing between years (i.e. missed appointments), the average of the preceding and following years was imputed for that year (total = 9/81 annual appointments were imputed (11%); 0/20 in Year 0, 3/20 Year −1, 3/16 Year −2, 1/12 Year −3, 2/8 Year −4, 0/5 Year −5). For patients with ‘still-idiopathic’ REM sleep behaviour disorder, Year 0 was set as the most recent evaluation.

Regression analysis was used to estimate the slope of progression over the prodromal period. Both linear and exponential slopes were calculated; linear results are presented in the figures, as they appeared to represent the progression pattern most accurately. To calculate the time at which results deviated from normal, the value at Year 0 in the regression was subtracted from the mean of normal control values—this value was then divided by the slope of the regression line to define the point of intersection. Patient values were compared with control values with the non-parametric Mann–Whitney U-test. To calculate potential diagnostic utility of motor measures, receiver operating characteristic curves were calculated comparing control values to patient values at Years 0, −1, −2 and −3. Optimal sensitivity and specificity were calculated for each value (optimal cut-off = highest value of sensitivity and specificity). Confidence intervals (90%) (i.e. defining the 5% upper and lower bounds) were calculated using the modified Wald method.

**Results**

Seventy-eight patients with idiopathic REM sleep behaviour disorder were included. During follow-up, 28 developed neurodegenerative disease, 22 of whom had parkinsonism according to UK Brain Bank criteria (the remaining six had dementia but did not meet diagnostic criteria for parkinsonism). One patient was excluded because full examination at diagnosis was impossible (he was institutionalized for his neurological condition 300 km from the examination centre), and one patient developed multiple system atrophy (during the revision stage of the paper); his results were not included. Two additional patients in the ‘still-idiopathic’ group reported new symptoms of neurodegeneration but have not yet been evaluated in person, and three have had only recent telephone follow-up—these were excluded from the analysis. Of the 20 patients, nine had also developed dementia within 1 year of parkinsonism diagnosis and were given a diagnosis of dementia with Lewy bodies; 11 were free of dementia within at least 1 year of diagnosis and had a diagnosis of Parkinson’s disease. Mean age at baseline was 70.5 ± 6.9 (73.8 ± 6.9 at parkinsonism diagnosis). Fifteen were male, five were female. Duration of REM sleep behaviour disorder symptoms at the time of baseline examination was 6.5 ± 4.0 years, with a 2.8 ± 3.0-year interval between initial polysomnographic diagnosis and baseline examination. During follow-up, four patients were diagnosed with parkinsonism at the second annual visit (i.e. Years −1 and 0 assessed), five were diagnosed at Year 3, three at Year 4, three at Year 5, two at Year 6, one at Year 7 and two at Year 8 (mean interval = 3.3 ± 1.8 years). UPDRS at baseline was 6.0 ± 4.9 in those who developed parkinsonism and 1.9 ± 2.0 in controls (P < 0.001). Mean age of controls was 70.1 ± 6.9, 30 were male and 10 were female.

**When does parkinsonism ‘start’?**

Progression of motor markers in the years before disease diagnosis is presented in Fig. 1. Since some patients with ‘still-idiopathic’ REM sleep behaviour disorder are probably in stages of preclinical parkinsonism, age-matched controls were used to estimate normal values. When compared with age-matched controls, the total UPDRS motor score in those who developed parkinsonism began intersected normal values an estimated 4.5 years before parkinsonism was defined (based on regression estimates). This deviation from normal values first reached statistical significance (on Mann–Whitney U-test) at 4 years before diagnosis (suggesting a minimum prodromal interval of 4 years).

The other quantitative motor tests, particularly the limb measures, seemed to intersect normal values at earlier time points than the UPDRS (Fig. 1 and Table 1). The Purdue Pegboard had the earliest estimated intersect, at 8.6 years, compared with 8.2 years for the alternate-tap test and 6.3 years for the timed up-and-go. However, except for the alternate-tap test, confidence intervals (CI) for these measures overlapped with the UPDRS confidence intervals, and
Figure 1  Progression of quantitative motor markers in the 5 years before diagnosis of parkinsonism. Year 0 is set at the year parkinsonism was diagnosed. Results of measures at the years before disease are set as Years —1 to —5. Error bars represent SD. Confidence intervals (90%) of the slope are represented by the thin dashed lines. Reference value is the mean control value (horizontal line). The number beside each point represents the number of observations at this time interval. *Significantly different from control values on the non-parametric Mann–Whitney U-test. (A) UPDRS, (B) alternate-tap test, (C) Purdue Pegboard and (D) timed up-and-go.

Table 1  Motor prodromal intervals

<table>
<thead>
<tr>
<th></th>
<th>Control values (n = 40)</th>
<th>Values at parkinsonism diagnosis—Year 0 (n = 20)</th>
<th>Slope (90% CI)</th>
<th>Estimated intersection point—years before diagnosis (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPDRS total</td>
<td>1.9</td>
<td>15.5</td>
<td>+3.05 (+ 2.46; +3.65)</td>
<td>4.5 (3.7, 5.6)</td>
</tr>
<tr>
<td>Purdue Pegboard (pegs/30 s)</td>
<td>11.7</td>
<td>9.4</td>
<td>−0.27 (−0.52; −0.027)</td>
<td>8.6 (4.5, 87.0)</td>
</tr>
<tr>
<td>Alternate-tap test (taps/min)</td>
<td>191.3</td>
<td>147.4</td>
<td>−5.33 (−8.91; −1.75)</td>
<td>8.2 (5.9, 20.2)</td>
</tr>
<tr>
<td>Timed up-and-go (s)</td>
<td>6.1</td>
<td>8.2</td>
<td>−0.33 (−0.53; −0.13)</td>
<td>6.3 (4.8, 12.4)</td>
</tr>
<tr>
<td>UPDRS—by location (voice/face)</td>
<td>0.106</td>
<td>1.14</td>
<td>+0.11 (± 0.029; +0.18)</td>
<td>9.8 (6.7, 29.8)</td>
</tr>
<tr>
<td>Axial—Gait</td>
<td>0.065</td>
<td>0.83</td>
<td>+0.11 (± 0.060; +0.16)</td>
<td>7.1 (5.6, 10.8)</td>
</tr>
<tr>
<td>Limb</td>
<td>0.110</td>
<td>0.59</td>
<td>+0.11 (± 0.089; +0.13)</td>
<td>4.3 (4.0, 4.8)</td>
</tr>
<tr>
<td>UPDRS—by cardinal manifestation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>0.074</td>
<td>0.85</td>
<td>+0.14 (± 0.11; ±0.18)</td>
<td>5.4 (4.8, 6.5)</td>
</tr>
<tr>
<td>Rigidity</td>
<td>0.052</td>
<td>0.61</td>
<td>+0.13 (± 0.083; +0.17)</td>
<td>4.4 (3.9, 5.5)</td>
</tr>
<tr>
<td>Gait</td>
<td>0.024</td>
<td>0.51</td>
<td>+0.11 (± 0.074; +0.15)</td>
<td>4.4 (3.9, 5.4)</td>
</tr>
<tr>
<td>Rest tremor</td>
<td>0</td>
<td>0.105</td>
<td>+0.08 (± 0.002; +0.16)</td>
<td>1.3 (1.0, 25.5)</td>
</tr>
</tbody>
</table>

Estimation of prodromal intervals for each outcome measure—the estimated onset corresponds to the point at which the linear regression curve crosses age-matched control values. Scores for the UPDRS subdivisions are the average scores from the corresponding UPDRS items.
Mann–Whitney U-tests also found statistically significant differences at 3 or 4 years before diagnosis; therefore, no significant differences between measures were evident. When curves were analysed with exponential models, intersect estimates were very similar to the linear model (4.3 years for UPDRS, 8.2 years for alternate-tap, 6.4 years for timed up-and-go and 8.8 years for Purdue Pegboard).

**Do progression patterns differ in location and type?**

When subdivided according to cardinal manifestations on UPDRS, all markers intersected normal values at similar time periods, except for rest tremor. The longest interval was for bradykinesia (5.4 years), followed by rigidity (4.4 years) and gait (4.4 years). Confidence intervals for each of these manifestations overlapped. Estimated rest tremor onset was only 1.3 years; however, only six patients had rest tremor at diagnosis, making this result imprecise. Bradykinesia scores were driven higher by voice and face; exclusion of these features reduced the estimate to 4.2 years (Fig. 2). When divided according to location, voice and face items seemed to intersect earliest (estimated interval 9.8 years, CI = 6.7, 29.8), followed by gait (7.1 years, CI = 5.6, 10.8) and limb features (4.3 years, CI = 4.0, 4.8) (Fig. 2 and Table 1). There was no difference in prodromal intervals between arms and legs; combining rigidity and bradykinesia scores, the interval was 4.63 years for the arms and 4.07 years for the legs.

**What are the sensitivity and specificity of motor markers?**

For each summary measure, the area under the curve (AUC) was calculated at diagnosis and for the three preceding years (Table 2). At the time of disease diagnosis, all measures could identify disease well, with AUC > 0.8 for all markers except for Purdue Pegboard. In the years before disease diagnosis, sensitivity and specificity of all measures declined, as expected. However, the alternate-tap test and (to a somewhat lesser extent) the Purdue Pegboard (AUC 0.67–0.796) were able to predict eventual diagnosis of parkinsonism (AUC > 0.8) even 3 years before diagnosis. At 3 years before diagnosis, the alternate-tap test could predict future diagnosis of parkinsonism with 79.5% sensitivity and 75.0% specificity, and the Purdue Pegboard predicted future diagnosis with 71.0% sensitivity and 81.8% specificity. The timed up-and-go test was relatively insensitive even at Year 0 (70.0%), and sensitivity continued to decline to a low of 46% at Year −3. UPDRS at a cut-off of >4 was a very good predictor of eventual parkinsonism diagnosis at 2 years before onset (87.5% sensitivity and 94.4% specificity), but sensitivity was only 54.5% at Year −3. Action tremor is common in non-parkinsonian conditions (such as enhanced physiological tremor, essential tremor); therefore, we assessed diagnostic utility if action tremor scores were removed from the UPDRS. Without action tremor, predictive value (particularly specificity) improved. At 2 years before onset, sensitivity was 93.8% and specificity was 97.2% with a cut-off of >3, and specificity of 100% could be obtained with a cut-off of >4 (sensitivity 87.5%).

**Does progression differ in Parkinson’s disease versus dementia with Lewy bodies?**

As we have previously reported, distinction between Parkinson’s disease and dementia with Lewy bodies was difficult; in our population there is considerable overlap in manifestations (Postuma et al., 2009c, 2011). Nonetheless, patients formally classified as Parkinson’s disease versus dementia with Lewy bodies demonstrated some differences in characteristics and in progression during prodromal stages (Fig. 3 and Table 3). Patients with Parkinson’s disease were younger than those with dementia with Lewy bodies (67.6 ± 7.6 versus 74.0 ± 6.2, P = 0.049). There were no differences in sex (Parkinson’s disease 7/11 male versus 8/9 male) or in the interval between baseline examination and disease diagnosis (3.2 ± 2.0 years versus 3.3 ± 1.9). In general, although measures were similar at time of diagnosis, progression of motor markers was slower in those who ultimately developed dementia with Lewy bodies. The estimated prodromal interval (i.e. intersect point) for UPDRS in Parkinson’s disease was 3.8 years (CI = 3.5, 4.2), compared with 6.0 years in dementia with Lewy bodies (CI = 4.3, 17.1). UPDRS progressed 3.9 points per year (CI = 3.0, 4.8) in prodromal Parkinson’s disease, compared with 2.1 (CI = 1.3, 2.8) in prodromal dementia with Lewy bodies. The estimated interval of the alternate-tap test was 5.8 years in Parkinson’s disease, compared with 11.4 years in dementia with Lewy bodies. The estimated interval of the Purdue Pegboard was 5.4 years in Parkinson’s disease, compared with 12.9 years in dementia with Lewy bodies. The timed up-and-go estimated interval was 3.8 s in Parkinson’s disease compared with 11.5 s in dementia with Lewy bodies. Note that estimates are imprecise, as numbers were low at long prodromal intervals.

**Motor results in ‘still-idiopathic’ REM sleep behaviour disorder**

As of the last visit, 48 patients with idiopathic REM sleep behaviour disorder had not been diagnosed with neurodegenerative disease. UPDRS at baseline was 2.7 ± 2.7 in these patients (P = 0.001 to those with parkinsonism, P = 0.13 to controls). Among these patients there was a mean 2.8 ± 2.1-year follow-up period. Overall, progression was slower in patients with ‘still idiopathic’ REM sleep behaviour disorder than in those who had developed parkinsonism (linear regression slope of UPDRS = 0.14; CI = −0.14, 0.43) points per year (Fig. 4). Since the slow progression could be due to floor effect (i.e. many patients have not developed mild prodromal parkinsonism, implying a progression rate of zero), we subdivided patients according to whether they manifested possible subthreshold parkinsonism in one of the last 2 years of follow-up, by using the best-performing index of prodromal parkinsonism (i.e. UPDRS > 3 excluding action tremor). Twelve patients had UPDRS > 3 (mean Year 0 UPDRS = 8.2) and 36 did not (mean UPDRS = 1.8). Although confidence intervals overlapped, their UPDRS progression rate appeared to be intermediate between...
the other patients with REM sleep behaviour disorder and those who developed clear parkinsonism [e.g. UPDRS slope = 0.64 (CI = 0.035, 1.25) versus 0.03 (CI = −0.14, 0.20) in the other patients with REM sleep behaviour disorder and 3.5 (CI = 2.5, 3.7) in the parkinsonism group]. Note that in this group, an exponential rate would be predicted since they may have some years early in follow-up with no parkinsonism at all. Consistent with this notion, mean UPDRS progression rate in the final 2 years for this group was 2.1 points, closer to progression rates in the parkinsonism group. Progression rates for alternate-tap test and Purdue Pegboard, however, did not appear to progress differently in patients with or without UPDRS > 3.

**Discussion**

Capitalizing upon the high rate of parkinsonism emerging from idiopathic REM sleep behaviour disorder, we were able to take an
unprecedented direct look at the progression of motor abnormalities before parkinsonism was diagnosed. Based on our analysis, we estimate that total UPDRS first becomes abnormal \( \sim 4.5 \) years before diagnosis. When divided according to location and cardinal manifestations, voice and face akinesia seem to be the first signs to develop, followed by rigidity, gait abnormalities, limb bradykinesia and finally tremor. Simple quantitative motor tests may be able to identify parkinsonism earlier than subjective examination.

Overall, our estimation of the duration of the prodromal motor interval of parkinsonism is similar to most estimates from dopaminergic imaging, whole brain glucose utilization imaging, neuropathological studies and assessments of motor progression in established disease (Fearonley and Lees, 1991; Vingerhoets et al., 1994; Moeller and Eidelberg, 1997; Morrish et al., 1998; Stoessl, 2007; Poewe and Mahlknecht, 2009; Fuente-Fernandez et al., 2011). Our direct motor assessment of prodromal motor parkinsonism therefore broadly confirms studies that have relied upon back-extrapolation in established disease. It is important to emphasize that this prodrome duration refers specifically to the measurable motor changes of prodromal parkinsonism; certainly non-motor features of the prodrome should be very different (indeed, this is the basis for this study, which relied upon REM sleep behaviour disorder as a way to identify patients in prodromal stages), and there may also be compensatory mechanisms in the striatum that allow preservation of normal motor function in the face of early stages of degeneration. It has been presumed that because of these striatal compensatory mechanisms, dopaminergic imaging should be more sensitive for detecting preclinical disease. In this regard, the similarity of prodromal interval estimates between our motor measures and standard dopaminergic neuroimaging measures are notable. Our findings could suggest that clinical motor manifestations and many dopaminergic imaging markers decline roughly in parallel, even in prediagnostic stages. This could suggest that [with the potential exception of newer techniques, such as dopamine turnover markers (Fuente-Fernandez et al., 2011)] there may not be much lead-time advantage of dopaminergic imaging over simpler quantitative testing for detection of prodromal parkinsonism. Of importance, sensitivity and specificity of subtle prodromal declines in dopaminergic imaging measures have never been systematically assessed, and preliminary evidence in idiopathic REM sleep behaviour disorder may suggest that sensitivity is suboptimal. In a recent study, dopaminergic single photon emission computed tomography missed 2/8 patients with preclinical parkinsonism with a prodromal interval of only 21 months (Iranzo et al., 2010). Follow-up studies of dopaminergic imaging in large-scale population studies are needed to define clinical utility of dopaminergic imaging as a prodromal marker.

In patients with established Parkinson’s disease the different cardinal motor manifestations progress at different paces; for example, gait and posture abnormalities generally develop later, whereas tremor is relatively non-progressive. In this analysis, we found only

### Table 2 Sensitivity and specificity of quantitative motor measures

<table>
<thead>
<tr>
<th>AUC</th>
<th>Optimal cut-off (value indicating disease)</th>
<th>Sensitivity % (90% CI)</th>
<th>Specificity % (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternate-tap</td>
<td></td>
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</tr>
<tr>
<td>Year 0 ((n = 20))</td>
<td>0.857</td>
<td>&lt;173</td>
<td>80.0 (64, 90)</td>
</tr>
<tr>
<td>Year – 1 ((n = 20))</td>
<td>0.865</td>
<td>&lt;176</td>
<td>80.0 (64, 90)</td>
</tr>
<tr>
<td>Year – 2 ((n = 16))</td>
<td>0.834</td>
<td>&lt;174</td>
<td>75.0 (67, 94)</td>
</tr>
<tr>
<td>Year – 3 ((n = 12))</td>
<td>0.808</td>
<td>&lt;176</td>
<td>79.5 (59, 92)</td>
</tr>
<tr>
<td>Purdue Pegboard</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 0</td>
<td>0.796</td>
<td>&lt;10.0</td>
<td>68.4 (49, 82)</td>
</tr>
<tr>
<td>Year – 1</td>
<td>0.790</td>
<td>&lt;10.5</td>
<td>75.0 (67, 94)</td>
</tr>
<tr>
<td>Year – 2</td>
<td>0.670</td>
<td>&lt;11.5</td>
<td>62.5 (42, 79)</td>
</tr>
<tr>
<td>Year – 3</td>
<td>0.792</td>
<td>&lt;11.0</td>
<td>71.0 (50, 85)</td>
</tr>
<tr>
<td>Timed up-and-go</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 0</td>
<td>0.852</td>
<td>&gt;7.5</td>
<td>70.0 (51, 84)</td>
</tr>
<tr>
<td>Year – 1</td>
<td>0.817</td>
<td>&gt;7.5</td>
<td>55.0 (37, 71)</td>
</tr>
<tr>
<td>Year – 2</td>
<td>0.803</td>
<td>&gt;7.5</td>
<td>50.0 (31, 69)</td>
</tr>
<tr>
<td>Year – 3</td>
<td>0.716</td>
<td>&gt;7.5</td>
<td>45.5 (24, 69)</td>
</tr>
<tr>
<td>Total UPDRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 0</td>
<td>1.0</td>
<td>&gt;8.5</td>
<td>100 (86, 100)</td>
</tr>
<tr>
<td>Year – 1</td>
<td>0.974</td>
<td>&gt;4</td>
<td>90.0 (73, 97)</td>
</tr>
<tr>
<td>Year – 2</td>
<td>0.941</td>
<td>&gt;4</td>
<td>87.5 (67, 97)</td>
</tr>
<tr>
<td>Year – 3</td>
<td>0.761</td>
<td>&gt;4</td>
<td>54.5 (31, 76)</td>
</tr>
<tr>
<td>Total UPDRS, excluding action tremor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 0</td>
<td>1.0</td>
<td>&gt;4</td>
<td>100 (86, 100)</td>
</tr>
<tr>
<td>Year – 1</td>
<td>0.986</td>
<td>&gt;3\textsuperscript{a}</td>
<td>95.0 (79, 100)</td>
</tr>
<tr>
<td>Year – 2</td>
<td>0.985</td>
<td>&gt;3\textsuperscript{a}</td>
<td>93.8 (75, 100)</td>
</tr>
<tr>
<td>Year – 3</td>
<td>0.792</td>
<td>&gt;3\textsuperscript{a}</td>
<td>54.5 (31, 76)</td>
</tr>
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</table>

\(\text{a At cut-off >4, sensitivity = 85%, specificity = 100% for Year – 1; sensitivity = 87.5%, specificity = 100% for Year – 2 and sensitivity = 45.5%, specificity = 100% for Year – 3.}\)
small differences in progression of the different cardinal findings in prodromal parkinsonism. The exceptions are voice and face abnormalities, which seemed to be present very early, and tremor, which had the shortest estimated pre-diagnostic interval. Tremor results should be viewed with caution, as only six patients had tremor at diagnosis. Also face/voice changes are quite subjective and do not factor strongly into diagnosis of parkinsonism—this could lengthen estimates of their prodromal interval.

Despite considerable effort, no clear neuroprotective therapy for neurodegenerative parkinsonism has been developed. One reason could be that at even early stages of clinical parkinsonism, the extent of dopaminergic neurodegeneration may be too extensive to show the impact of potential neuroprotective therapies (Lang, 2007). This has led to efforts to detect disease earlier—many potential markers, including olfaction, colour vision, transcranial ultrasound, dopaminergic imaging and sleep disorders have been proposed (Postuma et al., 2010). Based on our study, simple and inexpensive quantitative motor markers can now also be considered as prodromal markers, with reasonable sensitivity and specificity in prodromal stages. Since no studies have ever assessed diagnostic value of quantitative markers in prodromal parkinsonism, we cannot directly compare our results with previous research. However, one study assessing the unaffected side in established Parkinson’s disease found reasonable (but lower) AUC values of 0.73 with the Purdue Pegboard—other indices demonstrated lower diagnostic potential (Haaxma et al., 2010). Measuring the Purdue on the affected side, with disease duration of 1.2 years (i.e. later than our Year 0 assessment), sensitivity was 95% with 89% specificity (AUC 0.97). A combination of several other motor measures obtained an AUC of 0.82 in the affected limb. Two other groups (working in established Parkinson’s disease and in suspected Parkinson’s disease) found an AUC of 0.75–0.83 for tests of bradykinesia in the affected limb (Bohnen et al., 2008), and an AUC of 0.52–0.67 for a single wrist movement test (Montgomery et al., 2000a, b). An important advantage of the quantitative markers in our study is that unlike the UPDRS, they require no specialist training. On the other hand lead-time of all motor markers may be limited; the utility of our markers diminished considerably beyond 3 years prior to disease diagnosis.
Although dementia with Lewy bodies and Parkinson’s disease are extremely difficult to distinguish in our sample, we found some suggestions that parkinsonism in dementia with Lewy bodies may have a more indolent prodromal course. This is in accord with our informal subjective clinical observations—whereas numerous patients with Parkinson’s disease ‘surprised’ us by apparently developing motor findings quickly, many patients with dementia with Lewy bodies appeared to ‘linger’ with subtle bradykinesia for years before rigidity, tremor or gait instability eventually developed. The biological basis for this is unclear. Perhaps motor parkinsonism in dementia with Lewy bodies has a different (perhaps widespread) anatomical basis [as evidenced by its attenuated response to levodopa (Goldman et al., 2008)], and that regions outside of the substantia nigra degenerate more slowly. Alternatively, perhaps patients who develop Parkinson’s disease instead of dementia with Lewy bodies have a similar pattern of synuclein deposition, but have a more profoundly accelerated degeneration in response to synuclein in their substantia nigra—this would accelerate development of motor signs relative to non-motor features such as dementia (Postuma et al., 2009a).

This study includes a description of patients who, at last visit, were classified as ‘still-idiopathic’ REM sleep behaviour disorder. Note that for this group, results can be very complex to interpret, since it is likely to be heterogeneous. One could predict that there would be a group of patients with already-established subthreshold parkinsonism, another group in which no substantia nigra degeneration has yet developed (but will eventually start), and possibly another group who have REM sleep behaviour disorder that is not associated with synuclein-mediated degeneration. Mixing these groups together can produce unpredictable effects upon slope of progression. Using our best-performing measure of possible prodromal parkinsonism (i.e. UPDRS > 3 excluding action tremor) we found that 25% of our ‘still-idiopathic’ group were in possible prodromal stages of parkinsonism, whereas 75% showed no parkinsonism. Of course, any conclusions drawn from this group remain preliminary and need to be confirmed prospectively.

Our diagnosis of each syndrome was clinical, and we had approximately equal proportions of Parkinson’s disease and dementia with Lewy bodies. No patients in this cohort had a diagnosis of multiple system atrophy. However, multiple system atrophy is a difficult diagnosis to make early in the disease course, and our follow-up after diagnosis has ranged from only 1–5 years; therefore, some of our patients with Parkinson’s disease may in fact ultimately be diagnosed with multiple system atrophy. Of interest, we had two patients referred for idiopathic REM sleep behaviour disorder who developed motor symptoms of multiple system atrophy before polysomnogram could be performed (and therefore could not be included in this study)—this could possibly suggest that there could be a rapid progression to parkinsonism in multiple system atrophy.

Some limitations of this study should be noted. First, although a parkinsonism diagnosis was made by standard criteria applied by a movement disorders specialist, this nonetheless depended on subjective examination. Certainly, some examiners may have diagnosed parkinsonism a year earlier or later than the diagnosis was made. Secondly, precision of estimates at the longest intervals is limited by lower patient numbers—this is particularly important when patients are divided into subgroups (especially the distinction between Parkinson’s disease and dementia with Lewy bodies). Third, despite having examinations up to 5 years before parkinsonism, there was nonetheless some back-extrapolation required to estimate prodromal intervals > 5 years; these estimates should be considered imprecise. We estimated our prodromal intervals with linear regression, mainly because most markers
appeared to progress in a linear rather than exponential fashion. Certainly, progression may not be entirely linear (e.g. UPDRS progressed more rapidly from Year –1 to Year 0 than during other years). Of note, the UPDRS consists of a series of interrelated items rated on a 0–4 scale; therefore, scores may not decline linearly even with linear underlying neurodegeneration. And, in those who were ‘still-idiopathic’, one would predict an exponential curve due to floor effect at the longest prodromal intervals (i.e. if degeneration of substantia nigra has not yet started, the slope would be close to 0). However, the fact that our estimates required little or no back-extrapolation beyond actual observed values dramatically limits the effect of model selection. Indeed, estimates of the prodromal duration for the major indices were almost exactly the same in linear and exponential models. Calculations of the sensitivity and specificity of the motor measures should be interpreted as exploratory only, as they have been calculated for a single group, and have not been confirmed in a separate cohort. Although the prospective nature of this study implied that the examiner was blinded to eventual diagnosis of parkinsonism, there was no blinding to REM sleep behaviour disorder versus control status. Finally, parkinsonism is heterogeneous, and patients with associated REM sleep behaviour disorder may have different disease characteristics than those without; patients with Parkinson’s disease with REM sleep behaviour disorder in particular tend to have more cognitive impairment and autonomic dysfunction (Gagnon et al., 2009; Postuma et al., 2009b). Prodromal progression may be different in patients who do not have associated REM sleep behaviour disorder; in particular, the correlation between cognitive impairment and length of the prodromal motor interval suggests that patients with ‘pure’ motor Parkinson’s disease (i.e. with few non-motor features at onset, including REM sleep behaviour disorder) or young-onset patients (who rarely have cognitive impairment) may have shorter prodromal intervals. The need to rely upon

Figure 4 Progression of quantitative motor markers in the last 5 years of follow-up in patients who had idiopathic REM sleep behaviour disorder that had not converted to parkinsonism. The number beside each point represents the number of observations at this time interval. The diamond indicates the entire group, the triangles indicate those with possible prodromal parkinsonism at last follow-up (defined as UPDRS Part III >3, excluding action tremor) and the squares indicate those with no signs of possible prodromal parkinsonism. (A) UPDRS, (B) alternate-tap test, (C) Purdue Pegboard and (D) timed up-and-go.
a subgroup of Parkinson’s disease may be an unavoidable limitation—in a population-based study, to find 20 patients with incident parkinsonism would require 10,000 patients followed with annual neurologist examination for 5 years; currently, no such studies are being performed.

In conclusion, using direct assessment of motor examination before parkinsonism in REM sleep behaviour disorder, we have estimated a prodromal interval of ~4.5 years on the UPDRS; other quantitative markers may detect parkinsonism earlier. Simple quantitative motor measures may be capable of reliably detecting parkinsonism, even before a clinical diagnosis can be made by experienced movement disorders neurologists.

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