Title:
Motor dysfunction as a prodrome of Parkinson’s disease

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Abstract

Background
Recognition of motor signs in the prodromal stage, could lead to best identify populations at risk for developing Parkinson’s disease

Objective
This study identified motor symptoms and signs in individuals suspected of having Parkinson’s disease (PD) but who did not have a progressive reduction in the speed and amplitude of finger tapping or other physical signs indicative of bradykinesia.

Methods
146 patients, who had symptoms or signs suggestive of PD, were serially evaluated by a movement disorder specialist, using the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part I and video recordings. If the patients ‘converted’ to PD during follow-up, they were categorized as cases and compared with those who did not meet PD criteria during follow-up (non-cases).

Results
The 82 cases were more likely to have action dystonia or postural/action/rest tremor of a limb (OR 2.8; 95%CI 1.10 – 7.09; p=0.02), a reduced blink rate at rest (OR 2.32; 95%CI 1.18 – 4.55; p=0.01), anxiety (OR 8.91; 95%CI 2.55 – 31.1; p<0.001), depression (OR 7.03; 95%CI 2.86 – 17.2; p<0.001), or a frozen shoulder (OR 3.14; 95%CI 1.58 – 6.21) than the 64 ‘non-cases’. A reduction of the fast blink rate was common in patients who met the criteria for PD (p<0.001).

Conclusions
This study emphasizes that motor dysfunction is a component of the clinical prodrome seen in some patients with PD.

Keywords: Parkinson`s disease; prodrome; motor dysfunction
1.1 Introduction

The recognition of non-motor symptoms and early motor signs in the prodromal phase of Parkinson’s disease (PD) is an important academic initiative driven by the notion that, when neuroprotective treatments eventually become available, such individuals might be the best group to target for clinical trials (1).

The diagnosis of PD requires the presence of bradykinesia (reduction in speed and amplitude of finger tapping over 20 seconds) and the presence of rigidity and/or rest tremor (2-4). These cardinal signs need to be distinguished from mild extrapyramidal signs including slowness in the elderly and psychomotor retardation in severe depression (5-7). Subtle motor dysfunction, that may have been transient, can often be suspected in hindsight or after the review of historical copies of handwriting and family videos (8-11). A strong family history of PD or tremor, loss of sense of smell, REM sleep behavior disorder, refractory constipation and a history of severe depression also increase the risk of developing PD (12-16).

Between 2007 and 2008, we examined newly-referred patients with motor and non-motor symptoms for objective signs of motor dysfunction. We included people with complaints of slowness, symptoms of depression or anxiety, disturbed temperature regulation with excessive sweating, asymmetric postural tremor, orthostatic hypotension, urinary incontinence, hyposmia, REM sleep disorder, and shoulder frozen (17-23). Subtle objective motor abnormalities at baseline were identified and included 'suggestive' signs such as clumsiness, slowness or focal stiffness, and non-specific signs (see Table 1) (24, 25). We then followed this group prospectively with the hope of better characterizing the pre-diagnostic motor phase of PD.

1.1.2 Materials and Methods

The follow-up phase of the study was conducted at the Movement Disorders Outpatient Unit of the Neurology Department, Eugenio Espejo Hospital (a national reference center) in Ecuador, between 1 January 2009 to 1 January 2016. In accordance with the Declaration of Helsinki, the local research ethics committee approved the study and all participants provided written informed consent.

One hundred and fifty patients referred mainly by neurologists and general physicians, but also some self-referrals, were assessment at baseline for signs of parkinsonism. Four patients were excluded (26,27); one of these had hemidystonia, one had probable vascular parkinsonism and two had symmetric postural / action tremor with dystonia. One hundred and forty-six patients were enrolled in the study because they fulfilled the following criteria: attended the baseline visit; free from overt parkinsonism and dementia at the baseline
assessment; had one ‘suggestive sign of parkinsonism and at least one ‘non-
specific’ sign feature, with one or more non-motor symptoms (see Table 1).

Assessment was undertaken at the first consultation and then every 3 months,
and included a clinical examination by a neurologist specializing in movement
disorders (FA). All patients were evaluated with the UPDRS Part I-II-III (28).
Dexterity was evaluated using fine and alternating movements (finger tapping,
pronation and supination of the hand for one minute). Clinical examinations
were recorded on video. The blink rate was observed (both at rest and on fast
voluntary blinking) (29). The two test conditions were: (1) resting blink rate was
counted and (2) the patient was asked to look straight ahead and blink as fast
as possible for 1 minute. Blinks were counted as full blinks if at least 50%
closure of the eye occurred. Participants were asked about a family history of
PD and tremor (30,31). Information about early motor and non-motor
manifestations for possible PD was also gathered using a questionnaire. The
Hamilton depression and anxiety scales and the Mini Mental State Examination
(MMSE) (32-34) were applied with standardized scales in all patients by a
neuropsychologist. Magnetic resonance imaging (MRI) with T2 FLAIR and
diffusion-weighted imaging was performed on all patients at baseline, and did
not suggest any structural causes for the presenting complaints. A sleep
medicine expert asked during the interview if the patient had sleep disturbances
including, REM sleep behavior disorders, excessive daytime sleepiness (EDS),
insomnia and parasomnias. We asked during the interview if patients recall loss
or reduction in their smell and if they struggle with discrimination and
identification of odors.

All patients were followed-up for a minimum of 1 year. If in the course of follow-
up, the patients developed PD fulfilling clinical criteria (2,35) then they were re-
categorized as cases. Those participants who did not meet PD clinical criteria
remained as non-cases for the analysis. The last follow-up visit was when a
diagnosis PD was made for cases and the visit after which the observation
period finished for non-cases

In six patients we confirmed the diagnosis of PD with a levodopa challenge test.
One patient, who was diagnosed with PD had the diagnosis revoked during
follow-up and dopaminergic treatment was stopped. The patient then worsened
and reverted to take levodopa. During the follow-up of the 82 converted patients
to PD, the diagnosis was revised to progressive supranuclear palsy in one case,
multiple system atrophy in one, corticobasal degeneration in one and Lewy
body dementia in two patients

Statistical analysis

The data collected were expressed as the frequency (percentage) for
categorical variables and mean ± standard deviation for continuous numerical
variables. A comparison between cases and non-cases was done for
demographic and clinical data at baseline as well as UPDRS score at baseline
and at the last follow-up time. The categorical data were compared with z-test. Continuous data were compared by unpaired Student’s t-test. The tests were carried out with a two-tailed statistical significance level set at p=0.05.

For exploratory purposes, a nested case-non case analysis (unmatched) was performed to estimate the association between some clinical features of interest, including potential risk factors for PD at baseline, and the development of PD.

Odds ratios (ORs), 95% CI) and p-values were calculated for these variables considering the clinical conditions as predictors and PD patients as cases. The statistical analysis was performed with SAS9.3 software.

1.1.3 Results

One hundred and forty-six patients (48 females, 98 males) who met the inclusion criteria set out described in Table 1 participated in follow-up. All of them had subtle motor dysfunction or extrapyramidal signs at baseline (i.e. a combination of suggestive and non-specific motor signs on neurological examination). The patients had a mean follow-up duration of four years (range 1-7 years). The clinical features of these patients are summarized in Table 2.

Eighty-two patients (27 females and 55 males) were diagnosed with PD during the follow-up period. Their age at the onset of motor symptoms (59.4 ± 14.7 vs 56.0 ± 17.1; p=0.19) and at the baseline study visit (63.4 ± 11.9 vs 59.7 ± 15.4; p=0.10) tended to be greater. The average time between the date of registration with the study and the diagnosis of PD was 3.1 years. At the last follow-up visit, the age of converters was higher than in the non-converters (68.5 ± 12.0 vs 64.3 ± 15.1; p=0.06) (Table 2). The follow-up time during the study was similar in the PD patients (5.1 ± 1.4 vs 4.7 ± 1.1; p=0.03). When comparing the two groups, there was no difference in the frequency of a family history of PD (25.6% vs. 28.1%) or tremor (18.3% vs. 20.3%), and none of the patients had a family history of dystonia.

Baseline symptoms features were similar in the two groups, including clumsines (42% vs 39 45%), slowness of movement (28% vs 25 33%), stiffness (27% vs 22%) (Table 3), action dystonia or tremor of a limb (7% vs 5%), slow blink rate at rest (28 4% vs 25 3%), tremor (87% vs 89%), UPDRS I (1.05 ±0.9 vs 0.8±0.8), and UPDRS II (8.5 ±3.1 vs 8.0 ±3.4) were no different (Table 3). Only stiffness (27% vs 22%) and UPDRS III 9.4 ± 1.8 vs 8.7 ± 2.0) showed small differences between groups at baseline (Table 3). RBD and other combined sleep disorders (46 vs 19 52 %)were different. Constipation (38% vs 42%), hyposmia (28 % vs 31%), hypogeusia (17% vs 17%) and, action dystonia or tremor of a limb (7% vs 5%), frozen shoulder (17% vs 9%) showed no clear group differences at baseline., slow blink rate at rest (28 4% vs 25 3%), and tremor (87% vs 89%) (Table 3).
At the last follow-up assessment tremor and dystonia triggered by action were more frequently seen in patients who were diagnosed with PD in during that visit (25.6% vs 10.9%; p=0.02) (Table 4). and reduction in speed and or amplitude of finger tapping was also more common in those who developed PD (50% vs 36%; p < 0.03). Four patients showed dystonia of the foot after prolonged physical activity; one during swimming and another complained of dystonic cramping of the hand while playing the drums. Reduced mean blink rate at rest was also more frequent in the cases that were diagnosed with PD than in non-cases (55% vs 34%; p=0.01) (Table 4.3).

In the last follow-up visit after which the observation period finished for non-cases, one hundred twenty-nine patients (88%) also had early non-motor symptoms. Frozen shoulder (capsulitis) (62% vs 34%; p<0.001), depression (46% vs 11%, p<0.001), REM and other combined sleep disorders (46% vs 19% <0.0005) and anxiety (31% vs 5%; p <0.001) in the PD cases were all more frequent, constipation, hyposmia, hypogeusia did not showed changes in relation to baseline (table 4.3)

In the baseline evaluation with UPDRS (Parts I-III) (18.4 ± 4 vs 17.4 ± 5.18), we did not find any difference between cases and non-cases. When comparing UPDRS scores from the last assessment to the baseline assessment, greater changes were observed in the cases that were diagnosed with PD during follow-up; UPDRS (Parts I-III) (33.6 ± 9.1 vs 23.5 ± 7.2; p<0.001) and UPDRS motor (Part III) (19.1 ± 5.3 vs 11.7 ± 2.8; p<0.001).

Bradykinesia was, as expected, present in patients that converted to PD (100% vs. 33%; p <0.001), and rest tremor (88% vs. 9%; p <0.001) and rigidity (82% vs. 22%; p <0.001) were also common, compared to the non-cases.

Comparison of fast blink rate between baseline (95.2 ± 24.2 vs 98.7 ± 30.4, p=0.43) and last assessment fast blink rate (80.2 ± 24.6 vs 96.0 ± 30.6, p<0.001), showed clear deterioration in rate in patients who met the criteria for PD during follow-up compared with non-cases.

In the last follow-up visit, an association was found between the presence of action dystonia of a limb /tremor postural/action/rest of a limb (OR 2.8; 95%CI 1.1 – 7.1; p=0.02) (Table 5) and reduced blink rate at rest (OR 2.3; 95%CI 1.2 – 4.6; p=0.01), and the development of PD (table 4).

In the last follow-up visit non-motor symptoms, the probability of developing PD was higher when patients presented with anxiety (OR 8.9; 95%CI 2.6 – 31; p<0.001), depression (OR 7.0; 95%CI 2.9 – 17.2; p<0.001), and if they had symptoms of a frozen shoulder (OR 3.1; 95%CI 1.6 – 6.2, p<0.001) (Table 4).

1.1.4 Discussion
We followed a group of patients referred to a hospital neurological department with suspected parkinsonism. Patients who were subsequently diagnosed with PD during follow-up showed subtle motor signs for a mean 3.1 years before a diagnosis was made (2,9-14).

The age at diagnosis of PD was similar to that reported in other studies and was similar than that of the participants who did not develop PD (28,29,36). The proportion with a positive family history of PD was similar in the two groups, but was higher than that reported in most other published studies (28,29).

A frozen shoulder (capsulitis) is a well-recognized harbinger which can precede a diagnosis of PD by several months or even years (9,17,24,39). 62.2% of the cases in this series had pain and stiffness with limited movement at the shoulder, which is a higher percentage than that reported in other series and may relate to akinesia (9,17,40).

Tremor was the commonest motor symptom, present in 86.6% of patients with PD, which is similar to that found in a previous study (28). In 79 patients who met the criteria for PD, the tremor was postural / action and in three patients a monosymptomatic rest tremor occurred. There is some evidence to support a link between asymmetrical postural and action tremor and PD (19,20,28). In our series, all the patients with asymmetric tremor who developed PD also had additional subtle motor signs (19,28,29). Focal dystonia brought on by action and most frequently affecting the toes and foot (dystonic claudication) was also common at the time that patients were diagnosed with PD. This is already recognized as presenting feature of young onset Parkinsonism (idiopathic and monogenetic forms) (21,23), but was also noted in our study.

Reduction in resting blink rate is common in PD (22,40,41). It has been suggested that there is a link between the average spontaneous blink rate at rest and striatal dopaminergic function (22,41,42). We found a reduced blink rate at rest in 54.9% of the cases and a slowing of repetitive voluntary blinking performed over one minute (27). Previous studies have suggested reduced spontaneous blinking as an early sign of PD (22,41,42). Further studies are required to validate the ‘fast blink test’ to confirm its utility in early PD.

UPDRS III is a poor discriminator between soft extrapyramidal signs in the elderly, depression and those individuals who meet diagnostic criteria for Parkinson’s disease, but changes in motor scores over time may be a useful pointer. In our study action dystonia or tremor of a limb and reduced blink rate were other symptoms associated with a higher risk of developing PD (19-23,40-42).

Many cohort studies have evaluated the progression of the prodromes of PD using scales that were designed for use in established PD (43,44). The design of our study allows a much broader capture of clinical observations of motor dysfunction, years before patients met the criteria for PD. This in turn might help the field develop better quantitative scales that better capture motor dysfunction in the prodrome. The limitations of the study include the short follow-up period,
limited information by not to use potential bias due to not using standardized scales on for some motor and non-motor manifestations, as well as the lack of a control group that would allow a better understanding of the motor dysfunction trajectory.

More than half our cases converted to PD during follow-up indicating that the study group already had a very high risk of developing PD at the time of hospital referral. This study further emphasizes that some subtle motor signs and symptoms may occur years before overt bradykinesia can be identified clinically in PD and emphasizes that these need to be looked for as carefully identified with similar care as non-motor symptoms in studies designed to identify at risk groups. The results perhaps cast doubt on Braak’s hypothesis as a unifying explanation to the pathological staging of Parkinson’s disease (45,46).

Conflict of Interest

The authors have no conflict of interest to report.
1.1 Introduction

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Between 2007 and 2008, we examined newly-referred patients with motor and non-motor symptoms for objective signs of motor dysfunction. We included people with complaints of slowness, symptoms of depression or anxiety, disturbed temperature regulation with excessive sweating, asymmetric postural tremor, orthostatic hypotension, urinary incontinence, hyposmia, REM sleep disorder, and shoulder frozen (17-23). Subtle objective motor abnormalities at baseline were identified and included ‘suggestive’ signs such as clumsiness, slowness or focal stiffness, and non-specific signs (see Table 1) (24, 25). We then followed this group prospectively with the hope of better characterizing the pre-diagnostic motor phase of PD.

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assessment; had one ‘suggestive sign of parkinsonism and at least one ‘non-specific’ feature, with one or more non-motor symptoms (see Table 1).

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All patients were followed-up for a minimum of 1 year. If in the course of follow-up, the patients developed PD fulfilling clinical criteria (2,35) then they were re-categorized as cases. Those participants who did not meet PD clinical criteria remained as non-cases for the analysis. The last follow-up visit was when a diagnosis PD was made for cases and the visit after which the observation period finished for non-cases.

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Statistical analysis

The data collected were expressed as the frequency (percentage) for categorical variables and mean ± standard deviation for continuous numerical variables. A comparison between cases and non-cases was done for demographic and clinical data at baseline as well as UPDRS score at baseline.
and at the last follow-up time. The categorical data were compared with z-test. Continuous data were compared by unpaired Student's t-test. The tests were carried out with a two-tailed statistical significance level set at p=0.05.

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Baseline features were similar in the two groups, including clumsiness (42% vs 39 %), slowness of movement (28% vs 25 %), action dystonia or tremor of a limb (7% vs 5%), slow blink rate at rest (28 4% vs 25 3%), tremor (87% vs 89%), UPDRS I (1.05 ±0.9 vs 0.8±0.8), and UPDRS II (8.5 ±3.1 vs 8.0 ±3.4) were no different (Table 3). Only stiffness (27% vs 22%) and UPDRS III 9.4 ± 1.8 vs 8.7 ± 2.0) showed small differences between groups at baseline (Table 3). RBD and other combined sleep disorders (46 vs 19 %)were different. Constipation (38% vs 42%), hyposmia (28 % vs 31%), hypogeusia (17% vs 17%) and frozen shoulder (17% vs 9%) showed no clear group differences at baseline., slow blink rate at rest (28 4% vs 25 3%), and tremor (87% vs 89%) (Table 3).

At the last follow-up assessment tremor and dystonia triggered by action were more frequently seen in patients who were diagnosed with PD during that visit.
Four patients showed dystonia of the foot after prolonged physical activity; one during swimming and another complained of dystonic cramping of the hand while playing the drums. Reduced mean blink rate at rest was also more frequent in the cases that were diagnosed with PD than in non-cases (55% vs 34%; p=0.01) (Table 4).

In the last follow-up visit after which the observation period finished for non-cases, one hundred twenty-nine patients (88%) also had non-motor symptoms. Frozen shoulder (capsulitis) (62% vs 34%; p<0.001), depression (46% vs 11%, p<0.001), RBD and other combined sleep disorders (46% vs 19% <0.0005) and anxiety (31% vs 5%; p <0.001) were all more frequent in the PD cases, constipation, hyposmia, hypogeusia did not showed changes in relation to baseline (table 4).

When comparing UPDRS scores from the last assessment to the baseline assessment, greater changes were observed in the cases that were diagnosed with PD during follow-up: UPDRS (Parts I-III) (33.6 ± 9.1 vs 23.5 ± 7.2; p<0.001) and UPDRS motor (Part III) (19.1 ± 5.3 vs 11.7 ± 2.8; p<0.001).

Bradykinesia was, as expected, present in patients that converted to PD (100% vs. 33%; p <0.001), and rest tremor (88% vs. 9%; p <0.001) and rigidity (82% vs. 22%; p <0.001) were also common, compared to the non-cases.

Comparison of fast blink rate between baseline (95.2 ± 24.2 vs 98.7 ± 30.4, p=0.43) and last assessment fast blink rate (80.2 ± 24.6 vs 96.0 ± 30.6, p<0.001), showed clear deterioration in rate in patients who met the criteria for PD during follow-up compared with non-cases.

In the last follow-up visit, an association was found between the presence of action dystonia of a limb /tremor postural/action/rest of a limb (OR 2.8; 95%CI 1.1 – 7.1; p=0.02) (Table 5) and reduced blink rate at rest (OR 2.3; 95%CI 1.2 – 4.6; p=0.01), and the development of PD (table 4).

In the last follow-up visit non-motor symptoms, the probability of developing PD was higher when patients presented with anxiety (OR 8.9; 95%CI 2.6 – 31; p<0.001), depression (OR 7.0; 95%CI 2.9 – 17.2; p<0.001), and if they had symptoms of a frozen shoulder (OR 3.1; 95%CI 1.6 – 6.2, p<0.001) (Table 4).

1.1.4 Discussion

We followed a group of patients referred to a hospital neurological department with suspected parkinsonism. Patients who were subsequently diagnosed with PD during follow-up showed subtle motor signs for a mean 3.1 years before a diagnosis was made (2.9-14).

The age at diagnosis of PD was similar to that reported in other studies and was similar than that of the participants who did not develop PD (28,29,36).
proportion with a positive family history of PD was similar in the two groups, but was higher than that reported in most other published studies (28,29).

A frozen shoulder (capsulitis) is a well-recognized harbinger which can precede a diagnosis of PD by several months or even years (9,17,24,39). 62.2% of the cases in this series had pain and stiffness with limited movement at the shoulder, which is a higher percentage than that reported in other series and may relate to akinesia (9,17,40).

Tremor was the commonest motor symptom, present in 86.6% of patients with PD, which is similar to that found in a previous study (28). In 79 patients who met the criteria for PD, the tremor was postural / action and in three patients a monosymptomatic rest tremor occurred. There is some evidence to support a link between asymmetrical postural and action tremor and PD (19,20,28). In our series, all the patients with asymmetric tremor who developed PD also had additional subtle motor signs (19,28,29). Focal dystonia brought on by action and most frequently affecting the toes and foot (dystonic claudication) was also common at the time that patients were diagnosed with PD. This is already recognized as presenting feature of young onset Parkinsonism (idiopathic and monogenetic forms) (21,23), but was also noted in our study.

Reduction in resting blink rate is common in PD (22,40,41). It has been suggested that there is a link between the average spontaneous blink rate at rest and striatal dopaminergic function (22,41,42). We found a reduced blink rate at rest in 54.9% of the cases and a slowing of repetitive voluntary blinking performed over one minute (27). Previous studies have suggested reduced spontaneous blinking as an early sign of PD (22,41,42). Further studies are required to validate the ‘fast blink test’ to confirm its utility in early PD.

UPDRS III is a poor discriminator between soft extrapyramidal signs in the elderly, depression and those individuals who meet diagnostic criteria for Parkinson’s disease, but changes in motor scores over time may be a useful pointer. In our study action dystonia or tremor of a limb and reduced blink rate were other symptoms associated with a higher risk of developing PD (19-23,40-42).

Many cohort studies have evaluated the progression of the prodromes of PD using scales that were designed for use in established PD (43,44). The design of our study allows a much broader capture of clinical observations of motor dysfunction, years before patients met the criteria for PD. This in turn might help the field develop better quantitative scales that better capture motor dysfunction in the prodrome. The limitations of the study include the short follow-up period, potential bias due to not using standardized scales for some motor and non-motor manifestations, as well as the lack of a control group that would allow a better understanding of the motor dysfunction trajectory.

More than half our cases converted to PD during follow-up indicating that the study group already had a very high risk of developing PD at the time of hospital referral. This study further emphasizes that some subtle motor signs and
symptoms may occur before overt bradykinesia can be identified clinically in PD and emphasizes that these need to be looked for as carefully identified with similar care as non-motor symptoms in studies designed to identify at risk groups.

Conflict of Interest
The authors have no conflict of interest to report.
References


Table 1

Inclusion criteria in patients with pre-diagnosis of Parkinson’s disease

At least one ‘suggestive’ sign of parkinsonism

Patients with motor dysfunction including clumsiness, slowness or stiffness on neurological examination, who did not have a progressive reduction in the speed and amplitude of finger tapping performed over 20 seconds.

AND one non-specific feature

Patients with continuous or intermittent, familial or sporadic, unilateral or markedly asymmetric, postural, kinetic or intention tremor

Patients with familial Parkinson’s disease

Reduced blink rate at rest (< 20 blinks/during one minute)

Action dystonia of a limb or postural/action/rest tremor of a limb

Unexplained falls

Postural instability

PLUS, one or more early non-motor manifestations

Constipation, with bowel movements every 48 hours or more

Complaints of impaired sense of smell (hyposmia)

Complaint of diminished taste (hypoguesia)

REM-associated behavioral disorders (RBD) and other sleep disorders

Frozen shoulder

Depression: Hamilton test; score range >20 points (moderate to severe)

Anxiety: Hamilton test; score range >24 points (moderate to severe)
### Table 2. Baseline and follow-up demographic data in cases and non-cases

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Cases</th>
<th>Non-cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last visit (mean SD)</td>
<td>66.1±13.8</td>
<td>68.5±12.0</td>
<td>64.3±15.1</td>
</tr>
<tr>
<td>Male</td>
<td>98(67.1%)</td>
<td>65(67.1%)</td>
<td>43(67.2%)</td>
</tr>
<tr>
<td>Age at onset of symptoms (mean SD)</td>
<td>57.9 ± 15.8</td>
<td>59.4±14.8</td>
<td>56.0±17.1</td>
</tr>
<tr>
<td>Age at baseline (mean SD)</td>
<td>61.8±13.6</td>
<td>63.4±11.9</td>
<td>59.7±15.4</td>
</tr>
<tr>
<td>Age at onset of Parkinson’s disease (mean SD)</td>
<td>66.5±11.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up years (mean SD)</td>
<td>4.9±1.5</td>
<td>5.1±1.4</td>
<td>4.7±1.1</td>
</tr>
<tr>
<td>Family history of Parkinson’s disease</td>
<td>39(26.7%)</td>
<td>21(25.6%)</td>
<td>18(28.1%)</td>
</tr>
<tr>
<td>Family history of tremor</td>
<td>28(19.2%)</td>
<td>15(18.3%)</td>
<td>13(20.3%)</td>
</tr>
</tbody>
</table>

**Cases= Patients who met criteria of Parkinson’s disease**

**Non-cases=Patients who not met criteria Parkinson’s disease**
<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Cases</th>
<th>Non-cases</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[n=146 (100 %)]</td>
<td>[n=82 (54.7 %)]</td>
<td>[n=64 (45.3 %)]</td>
<td></td>
</tr>
<tr>
<td>Slowness</td>
<td>44 (30.13)</td>
<td>23 (28.0)</td>
<td>16 (25.0)</td>
<td>0.68</td>
</tr>
<tr>
<td>Clumsiness</td>
<td>64 (43.83)</td>
<td>35 (42.68)</td>
<td>25 (39.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Stiffness</td>
<td>42 (28.76)</td>
<td>24 (29.27)</td>
<td>14 (21.88)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>tremor / dystonia post fatigue</td>
<td>9 (6.16)</td>
<td>6 (7.32)</td>
<td>3 (4.69)</td>
<td>Ns</td>
</tr>
<tr>
<td>blinking at rest</td>
<td>39 (26.71)</td>
<td>23 (28.05)</td>
<td>16 (25.00)</td>
<td>Ns</td>
</tr>
<tr>
<td>Score UPDRS-I (mean SD )</td>
<td>0.93 ± 0.91</td>
<td>1.05 ± 0.93</td>
<td>0.81 ± 0.89</td>
<td>0.12</td>
</tr>
<tr>
<td>Score UPDRS-II (mean SD )</td>
<td>8.32 ± 3.30</td>
<td>8.57 ± 3.15</td>
<td>8.08 ± 3.45</td>
<td>0.36</td>
</tr>
<tr>
<td>Score UPDRS-III (mean SD)</td>
<td>9.09 ± 1.94</td>
<td>9.45 ± 1.83</td>
<td>8.73 ± 2.06</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Cases= Patients who met criteria of Parkinson’s disease  
Non-cases= Patients who not met criteria Parkinson’s disease
Table 4. Association between signs and symptoms in last time assessment in cases and non –cases

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total patients (%)</th>
<th>Total patients (%)</th>
<th>Total patients (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Non-cases</td>
<td>OR (IC 95%)</td>
<td></td>
</tr>
<tr>
<td>[n=82 (54.7 %)]</td>
<td>[n=64 (45.3 %)]</td>
<td>[n=146 (100 %)]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Early motor signs**

- Tremor/dystonia after action: Cases 21 (25.6), Non-cases 7 (10.9), OR 2.8 (1.10 – 7.09), P = 0.02
- Reduced blink rate at rest: Cases 45 (54.9), Non-cases 22 (34.4), OR 2.32 (1.18 – 4.55), P < 0.01

**Early non-motor signs**

- Frozen shoulder: Cases 51 (62.2), Non-cases 22 (34.4), OR 3.14 (1.58 – 6.21), P < 0.001
- Depression: Cases 38 (46.3), Non-cases 7 (10.9), OR 7.03 (2.86 – 17.2), P < 0.001
- Anxiety: Cases 25 (30.5), Non-cases 3 (4.7), OR 8.91 (2.55 – 31.1), P < 0.001
- REM and sleep disorders: Cases 38 (46.3), Non-cases 12 (18.8), OR 3.74 (1.74 - 8.02), P < 0.0005

*Cases= Patients who met criteria of Parkinson’s disease
Non-cases=Patients who not met criteria Parkinson’s disease*
Supplementary videos
We send the videos in previous version to the email jpd@iospress.com

Title:
Motor dysfunction as a prodrome of Parkinson’s disease

Videos

Patient 1

Prodromal video 1A. 70-year-old male, presenting right shoulder pain two years before diagnosis. Video shows slow blink with staring, and slowness for fine and alternating movements of right hand and right leg, with slight dystonic posture of the foot.

Parkinson’s disease video 1B. 77-year-old patient, after four years of L-dopa therapy, shows stooped posture, reduced arm swing and bradykinesia of the right hand.

Patient 2

Prodromal video 2A. 50-year-old woman, with history of constipation since childhood, intermittent asymmetric postural tremor and left shoulder pain eleven and three years before premotor diagnosis, respectively. Video shows slowness bilaterally, and clear awkwardness in performing movements with the left hand.

Pre-motor video 2B. 53-year-old patient shows reduction of fast blink rate and slowness and awkwardness in performing alternate movements with the left hand.

Parkinson’s disease video 2C. 58-year-old patient, four years after commencing therapy with L-dopa, shows rigidity and left bradykinesia.