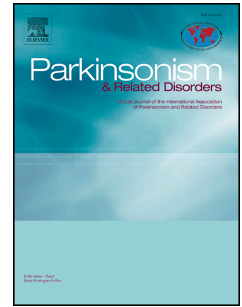


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Dysphagia predicts poor outcome in late-stage Parkinson's disease

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Abstract

Background: Few data exist on the rate of clinical progression for Parkinson's disease (PD) patients who have entered a late stage of the disease.

Objective: Study the clinical progression of a late-stage PD (LSPD) population over one year follow-up.

Methods: 50 LSPD patients (Schwab and England ADL Scale <50 or Hoehn Yahr Stage >3 in MED ON) underwent an extensive clinical assessment at baseline and after one year and an acute levodopa test at baseline.

Results: Mean age of LSPD patients (female 46%) was 77.5 ± 5.9 years and mean disease duration was 15.5 ± 6.5 years. At baseline, 76% had levodopa-induced motor complications (MC), usually non-troublesome, 68% were demented, 54% had psychosis and 68% depression. Caregiver distress was high. L-dopa responsiveness was mild ($18\% \pm 12$ of improvement on MDS-UPDRS-III). After one-year, 20% of the patients were dead, institutionalized or HY 5. MDS-UPDRS-motor mean score worsened 7.2 ± 10.3 points although there was heterogeneity between patients, and there was a global worsening of non-motor symptoms, mostly in cognition/mood, urinary and gastrointestinal domains. Nevertheless, MC improved despite similar levodopa equivalent dose. Functional independence and quality of life worsened. Dysphagia severity at baseline predicted a poor outcome (death, institutionalization or HY 5) (Hazard ratio 2.3, 95% CI 1.12- 4.4; $p = 0.01$), whereas magnitude of L-dopa response of LSPD patients did not.

Conclusions: LSPD patients still present a significant, although heterogeneous, motor and non-motor progression over 1 year. Dysphagia severity predicts the occurrence of additional disease severity milestones and its management must be prioritized.

Introduction

Progression in Parkinson's disease (PD) seems to be exponential in its later stages [1]. Indeed, a number of advanced PD patients enter a later stage when motor and non-motor symptoms (NMS) such as falls and dementia rapidly aggravate, causing a major impact on the health status and independence of patients [1, 2]. Nonetheless, scarce data exist on the rate of clinical progression and prognostic factors for patients who have already entered a late disease stage [3, 4]. Equally, uncertainty exists whether the magnitude of levodopa (L-dopa) responsiveness is a prognostic factor in late-stage PD (LSPD).

Our aim was to study the clinical progression and response to L-dopa in a LSPD sample over one-year follow-up.

Patients and methods

Primary objective

To study the clinical progression of a LSPD population over one year follow-up.

Secondary objective

To study the response of LSPD patients to a suprathreshold dose of L-dopa.

Study design and patients recruitment

We performed a cross sectional study and a prospective cohort study.

Patients were consecutively recruited from the Movement Disorders outpatient clinic of a tertiary university hospital. Idiopathic PD patients,

according to the “United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria” (UKBB) criteria [5], were included in the study if they had a Schwab and England score (S&E) < 50% [6] or a Hoehn & Yahr Stage (HY) >3 in “Medication ON” (MED ON). LSPD patients were assessed at baseline and at 1 year follow-up (range 12-15 months). The Local Ethical Committee approved the study and all patients provided informed consent.

Patients' assessment

At baseline, patients underwent an extensive clinical assessment including a challenge test. Details of L-dopa challenge test were previously reported [7, 8]. Basically, patients have been firstly assessed in “Medication OFF” (“MED-OFF”, after 12 hours overnight of anti-dopaminergic drug withdrawal) and secondly, in “MED ON” (after the intake of a supramaximal dose of L-dopa, 150% of the morning dose). Overall, during both “MED OFF” and “MED ON” conditions the following parameters were evaluated: a) motor performance using the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III scale [9], the Modified Abnormal Involuntary Movement Scale (mAIMS)[10] and the HY stage; b) the change of specific NMS: blood pressure (BP) measured in supine and 3 minutes after standing, presence of orthostatic hypotension (OH), pain and fatigue using a visual analogue scale (VAS-p and VAS-f, respectively). L-dopa equivalent daily dose (LEDD) was calculated according to standard conversions [11]. Clinical phenotypes, i.e. akinetic-rigid (AK) and tremor dominant (TD), were defined in concordance with

clinical history. NMS were evaluated using the MDS-UPDRS part I, the Non-Motor Symptoms Assessment Scale for PD (NMSS) [12], the Neuropsychiatric Inventory test (NPI) 12-items and the Geriatric Depression Scale (GDS) MDS-UPDRS parts II and IV assessed the impact of motor symptoms on activities of daily life (ADL) and L-dopa-induced motor complications (MCs), respectively. Diagnosis of PD with dementia (PDD) was made in agreement with the Level I algorithm of the MDS Task Force recommendation for PDD diagnosis [13]. Quality of life (QoL) and health-related (Hr) QoL were assessed using the PD questionnaire 8 (PDQ-8) [14] and the Visual Analogue Scale of the Euro-Qol-5D (EQ-5D VAS). Handicap and autonomy in ADL was assessed using the London Handicap Scale (LHS) [15] and S&E [6], respectively. Caregivers' burden was assessed with the Zarit Caregiver Burden Inventory (ZCBI) [16] except in institutionalized patients, as a familiar caregiver was absent. At follow-up, patients repeated the same clinical assessment with the exception of the ZCBI and the L-dopa challenge test. After the L-dopa challenge test and at follow-up, Patients and investigator completed the Patient's Global impression-Improvement (PGI-I) and the Clinical Global Impression Improvement Scale (CGI-I), respectively. Assessments were performed at patients' home whenever required by patients' health status or caregiver preference.

Statistical Analysis

Descriptive statistics of demographic, clinical and therapeutic data were provided for continuous [mean and standard deviation (SD)] and categorical (count and percentage) variables.

The acute effect of L-dopa was calculated comparing the MDS-UPDRS Part III score or sub-items, the mAIMS, BP values, VAS-f, VAS-pain, and OH presence/absence in “MED OFF” versus “MED ON”, using the t-test, the chi-square test or Fischer’s exact test as appropriate, applying the Bonferroni’s correction for multiple comparisons. MDS-UPDRS-III sub-items for speech (item 3.1), resting tremor (item 3.17), rigidity (item 3.3), bradykinesia (sum of items: 3.4-3.8 and 3.14), posture (item 3.13), gait (item 3.10), freezing of gait (item 3.11), arising from chair (item 3.9), and postural instability (item 3.12) were studied separately. Correlations were tested using Pearson’s rank correlation coefficient.

For longitudinal analysis, time-course comparisons of paired data sets were performed using Student’s t-test (continuous variables) or chi-square (categorical variables) test, as appropriate. Death, being institutionalized de novo in a nursing home or progressing to HY 5 at one-year follow-up was considered as a combined outcome, whichever occurred first. We have performed two Kaplan-Meier survival analysis using two different outcomes; the first one explored time to the occurrence of death while the second analysed time to the occurrence of the combined outcome of death, institutionalization or HY 5. Differences in the estimated survival distribution stratified by presence of dementia, psychosis, gender, moderate/severe dysphagia (MDS.UPDRS item 2.3 >2), and PD phenotype (AK vs. TD) were examined using the log rank test. Statistically significant variables ($p < 0.05$) were then used as covariates in two Cox-proportional hazard regression models (model 1: dependent variable was death; model 2: dependent variable was the combined outcome of death, nursing home or HY 5). If a variable showed border statistical

significance ($0.045 < p < 0.055$), different Cox-proportional regression models were built and the one which minimized the Akaike information criterion [AIC: $2K - 2\ln(\hat{L})$, being k be the number of estimated parameters in the model and \hat{L} the maximum value of the likelihood function for the model] was selected. The following variables were entered in the regression model: age, gender, HY (MED OFF), SE (MED OFF), PDD, MDS-UPDRS-item 2.3 (dysphagia severity), and NMSS total score.

All p values reported are two-tailed and a $p \leq 0.05$ was considered statistically significant. Coefficients and 95% confidence intervals (CIs) are reported. SPSS 23.0 statistical software (SPSS, Chicago, IL) was used.

Results

Demographic and clinical data at baseline

From an initial sample of 135 HY 4-5 patients, fifty LSPD patients were included in the study, in agreement with inclusion/exclusion criteria and patients/caregivers' availability in participating in the study. Forty patients had a S&E $< 50\%$ while thirty-eight patients had a HY > 3 , and thirty-two fulfilling both criteria. Forty-six LSPD patients (92%) were observed at home or nursing home due to severe disability. All institutionalized patients lived in nursing homes and not in assisted living facilities, as they were mostly dependent in activities of daily living and needed medical care and supervision. Indeed LSPD patients presented a severe clinical picture with a high prevalence of disability milestones (dementia 68%, psychosis 56%, 2 falls per month, wheelchair-bound 18% and institutionalization in nursing homes 20%) and NMS (NMSS total score 118 ± 46.6 and NPI-12 total score 21.7 ± 16.2) which negatively affected

HR-QoL and caregiver's distress (ZBDS score 28.3 ± 13.3) (Table 1). 38 (76%) of LSPD patients had levodopa-induced MCs, which were troublesome only in about a third of the patients (Table 1). Patients with dementia had worse scores of MDS-UPDRS-III, NPI-12 items, NMSS, PDQ-8, LHS and S&E compared to non-demented LSPD patients ($p < 0.05$). PDQ-8 significantly correlated with NMSS and motor impairment ($R = 0.74$ and $R = 0.54$, $p < 0.01$).

LSPD disability progression

Mortality and combined poor outcome. At one-year follow-up (range 12-15 months) 10 (20%) LSPD patients were dead (Table 1). All dead patients were HY 4-5 at baseline. Kaplan Meier survival curves and the log-rank test showed statistical significant difference in the occurrence of the combined poor outcome (death, nursing home or progressing HY 5) for institutionalized patients at baseline ($p = 0.002$), patients who needed a formal caregiver ($p=0.006$) and those with moderate/severe dysphagia (MDS-UPDRS item 2.3 >2) ($p = 0.001$) (Figure 1 and Supplementary material: Table S1). Institutionalized patients, those with moderate/severe dysphagia and PDD patients at baseline had a significant poor outcome even when considering death as the single final event at follow-up ($p=0.01$; 0.003 ; 0.038 , respectively).

In multivariate Cox-proportional hazard regression analysis, dysphagia severity (MDS-UPDRS item 2.3) was the only variable that significantly predicted the occurrence of the combined outcome with a hazard ratio of 2.3 (1.1- 4.4, 95% CI; $p = 0.01$) (Table 2). Dysphagia severity was also the only

variable that predicted the occurrence of death with a hazard ratio of 2.9 (1.12- 8.6, 95% CI; $p=0.04$). Patients with PDD at baseline presented a more significant worsening of dysphagia at follow-up if compared to non-demented patients ($p=0.011$).

Motor and non-motor progression. Baseline mean MDS-UPDRS motor score of patients dead at follow-up was significantly worse compared to that of surviving patients, in both ON and OFF state (OFF: 78 ± 12.2 vs 65.5 ± 14.2 ; ON: 69.6 ± 15.6 vs 53.1 ± 14.6 , both $p = 0.02$). Four patients withdrew from the study (3 did not answer to phone calls and follow-up visits could be not scheduled and 1 withdrew informed consent). 36 LSPD patients were examined at one-year visit. During follow-up, 7 patients (14%) were hospitalized and 9 (22%) were institutionalized. Six cases (16%) changed from HY 2-4 to 5, nevertheless median HY stage did not change significantly, though dead patients had a significantly higher HY (OFF and ON) at baseline ($p < 0.05$) if compared to survivors. Compared to baseline, there was a statistically significant worsening of motor and non-motor disability, independence in ADL (including a significant worsening in eating tasks abilities, see Table 1), handicap and HR-QoL. Interestingly, neither the frequency of fallers nor the number of falls/month change significantly at follow-up, but more patients were wheelchair-bound ($p < 0.001$). The mean deterioration of motor score (MDS-UPDRS-III, MED ON) (N = 32) was 7.2 (± 10.0) points corresponding to a 15.7% (± 23.0) increase, with no difference between TD vs AK phenotype or patients with/without PDD at baseline. However, 12 patients (37,5%) had a motor deterioration ≤ 3 points and 14 (43%) ≤ 5 points. Eleven

cases (32%) did not deteriorate and, in fact, 10 of these improved between 1-6 points. The mean progression of MDS-UPDRS part II was significantly worse in patients aggravating > 5 points in the motor score compared to those worsening ≤ 5 points or improving in the MDS-UPDRS motor score (2.1 ± 4.1 vs -1.3 ± 2.9 , $p = 0.01$). The score of MDS-UPDRS part IV significantly improved at 1 year follow-up (mean -1.5 ± 3.8 points; $20 \pm 50\%$ decrease). Fewer patients had motor fluctuations and troublesome motor fluctuations, although there were significantly more patients with dyskinesias which nevertheless were less troublesome (Table 1).

The direction of change of NMS between baseline and follow-up differs among scales (Table 1). The total score of NMSS worsened significantly while MDS-UPDRS Part I and NPI did not. The frequency of PDD was similar but MMSE score worsened significantly, as did the scores of the items "Cognition" and "Memory" in MDS-UPDRS part I and NMSS, respectively. Despite 5 (13%) developing new psychosis, the number of patients with psychosis significantly decreased at follow-up although the scores of "Hallucinations" item in MDS-UPDRS part I, NMSS and NPI did not change. This finding may relate to the fact that 8/10 dead patients had baseline psychosis. The total score of GDS was similar between baseline and follow-up, although the score of "Depression" item in NPI worsened significantly. "Daytime sleepiness" and "Light headedness" (MDS-UPDRS part I) were significantly better at follow-up, as was the "Cardiovascular" domain of NMSS. The scores of "Urinary" significantly increased at follow-up in both MDS-UPDRS-I and NMSS (Table 1).

The score of MDS-UPDRS part II (N = 36) worsened 2.3 points (± 4.0) corresponding to a 6.0% (± 15.0) increase, and S&E scale also significantly deteriorated between baseline and follow-up. Handicap (LHS) as well as the HR-QoL measured by the EQ-5D-VAS was significantly worse after 1 year, although the change in the PDQ-8 was not significant (Table 1).

Levodopa acute challenge test

The mean MDS-UPDRS-III score was 68.1 (± 14.1) in MED OFF and 58.4 (± 15.5) in MED ON, with a significant median improvement of 18% (± 12) ($p < 0.001$) (Table 3). Sub-analysis of MDS-UPDRS-III scores showed a significant improvement with L-dopa for appendicular symptoms (rest tremor >> rigidity >> bradykinesia) while no significant changes were noted for axial signs (Table 3).

Measurement of BP in orthostatism was not possible in twelve patients (24%) (two had symptomatic OH, one an amputee leg and nine a severe postural instability). Mean change of SBP from supine to orthostatism as well as mean DBP in orthostatism were statistically different between MED OFF versus MED ON (Table 3). Four patients developed OH in MED ON, which was symptomatic in three (Table 3). 68% of the patients succeeded in completing the VAS scales: pain improved significantly after L-dopa intake, while fatigue did not (Table 3).

We found a significant correlation between the Δ AIMS and the Δ MDS-UPDRS-III score ($R = 0.64$; $p < 0.001$). Similarly, MDS-UPDRS-IV total score and dyskinesia/motor fluctuations severity sub-items (4.2 /4.5) had a

strong correlation with the Δ MDS-UPDRS-III score ($R= 0.63 /0.58$ respectively; $p<0.001$), whereas, though significant, the correlation was milder for dyskinesia/motor fluctuations duration sub-items (4.1 and 4.3) ($R=0.4/0.38$ respectively; $p<0.05$). No significant correlation was found between Δ MDS-UPDRS-III score and Δ VAS-p. Patients with PDD and AK phenotype had a poorer motor improvement with L-dopa ($p<0.05$). No correlations were found between Δ MDS-UPDRS-III score and PDQ-8, EQ-5D VAS, LHS, S&E and HY. The mean of the PGI-I and CGI-I scales was 3.1 (± 0.9) (“minimally improved”), though 12 patients were not able to answer. No serious AEs occurred during the test: eleven cases reported moderate drowsiness or fell asleep after L-dopa, three had symptomatic hypotension and two vomited (Table 3).

Discussion

We report the clinical progression of a LSPD cohort over one-year follow-up. After one year, the disease progressed significantly, affecting several motor and non-motor domains and about one-fifth of the cases were dead, institutionalized or changed to HY 5. Severity of dysphagia at baseline is the most important negative prognostic factor for the occurrence of death, institutionalization or HY 5.

As expected, LSPD patients had a high functional dependence, resulting in a severe caregiver distress. Indeed, all need a caregiver and one-fifth lived in nursing home which is possibly influenced by socio-cultural factors or healthcare system organization, although it is similar to that of the UK

(14%) and US (25%) [17, 18] but lower if compared to the Sydney cohort study at 20 years (48%) [4].

Unexpectedly, we found a high frequency (16%) of HY 2 patients among LSPD group, of whom all but one (with severe axial signs) had PDD with S&E score < 50%. This reflects a previously described limitation of the HY scale, which is heavily weighted toward postural instability [1, 19], and the fact that PD patients may become demented before losing balance. Our data reinforces the usefulness of the S&E scale to identify the whole spectrum of PD patients who entered a late disease stage. LSPD patients had a marked impairment in several NMS domains, with a predominance of urinary, cognitive and sleep disturbances [2, 20]. Frequency of dementia and psychosis is roughly comparable to our previous study [8], while depression frequency was lower, even though a fifth of the patients were not able to fill the GDS. This frequency rose 20% if taken into account questionnaires filled out with caregivers' help. When comparing our results to the Sydney Multicenter study, we find roughly comparable results for NMS, with a similar prevalence of psychosis (50%), depression (50%), urinary incontinence (around 70%), equivalent values for MMSE score after 15 years of disease (around 22) [21] and frequency of "occasionally choking" (around 50%), with no patient needing artificial feeding at baseline in both studies. Frequency of dementia was higher in the Sydney cohort (83%) [4], probably due to different criteria used to diagnose PDD or otherwise because the mean duration of PD in our study was shorter. Over one year, motor and non-motor scores of LSPD patients worsened significantly. Reported annual increase of motor impairment has been estimated around 2.4 points in the

UPDRS-III within the first five years of disease [22], with a standardized annual progression rate of 2.4% in intermediate disease stage [23]. Although a slower rate of progression has been reported in more advanced stages of PD [23], we found a steeper mean deterioration score at the MDS-UPDRS Part III score, highlighting that a faster disease course could take place in late disease phase. However, this is not homogenous as a considerable percentage of patients deteriorated less than 3 or 5 points, a range that includes the minimal clinically important difference value of this scale, identified as an increment of 4.68 points, and one-third did not worsen or even improved. This heterogeneity might be due to the death of patients in poorer motor condition during follow-up or medication adjustment after L-dopa test or, alternatively, may suggest that only a sub-group of LSPD patients rapidly evolves while stabilization or even improvement of symptoms is still possible. A faster progression of midline motor disability could explain the higher motor score deterioration found in our study [25]. The low rate of patients lost at follow-up (8%) and their similar baseline scores if compared to the other patients, would unlikely had an impact on our higher motor score progression. Annual progression rate of 2.2 points in UPDRS-II has been reported [23] for intermediate stage PD patients, which is similar to our findings. Interestingly, L-dopa induced MCs significantly decreased at follow-up despite similar LEDD, confirming the low frequency of troublesome MCs among LSPD [2, 7].

Among NMS, cognition/mood, urinary and gastrointestinal dysfunction progressed the most. Cardiovascular symptoms seem to decrease. A possible explanation could be the underestimation of these symptoms at follow-up

due to cognitive impairment, the fact that BP measurement was not possible in 24% of the cases, the fact that dead patients had a higher though not significant score for cardiovascular symptoms at baseline or because patients spend more time supine.

Institutionalized patients and those with more severe dysphagia have a higher risk of death, institutionalization or HY 5 within one year. Nursing home residents with PD may have a 30% higher mortality rate compared to community dwelling patients [26]. In many instances, those patients are under-treated for motor symptoms, although interventions could lead to significant improvements in functioning and QoL [20, 27]. LSPD patients in nursing homes are a fragile subgroup, whose treatment is particularly challenging, as expertise in the management of PD is not uniform among healthcare professionals of nursing homes. In multivariate analysis, only dysphagia severity predicts a poor outcome. Interestingly, despite a 28% frequency of severe dysphagia, only one patient had a gastrostomy. Nonetheless, the main confirmed death cause was pneumonia and one patient died due to food asphyxiation. As frequent pulmonary infections is the leading cause of death in PD [28, 29], our results stress the relevance of swallowing monitoring in LSPD patients. Of note, none of our patients had the chance to do swallowing therapy or aspiration pneumonia prevention strategies (data not shown), due to their difficulties in reaching a swallowing therapy centre.

Of note, the magnitude of acute L-dopa response does not predict progression of PD at this disease stage. This may be accounted for a floor effect. In fact, when the magnitude of L-dopa responsiveness decreases

below a certain level, its impact on patients' global functioning and disease progression is minimal. In this study, the magnitude of L-dopa responsiveness in LSPD was slightly higher compared to our previous findings (18% vs 11%; 12.7 vs 8.5 points) [7]. This difference could be attributed to a larger sample or the inclusion of a larger spectrum of LSPD patients (namely HY 2 cases), even if other clinical features are alike. The clinical significance of this better motor response is marginal according to the CGI-I/PGI-I and the change in the S&E between off and on state. Our results corroborate the unresponsiveness of axial signs to L-dopa in late stage. L-dopa response in LSPD patients was correlated with dyskinesias, adding evidence to our previous suggestion of cautiously increasing L-dopa dose in those patients manifesting MCs or in whom tremor or rigidity are the most troublesome signs [7]. LSPD patients with AK phenotype or PDD had a worse response to L-dopa, which is contrary to previous findings [25, 30]. However, the adoption of different definitions for cognitive impairment and TD phenotype may explain the divergent results [25].

The strength of our study is to couple data on L-dopa responsiveness with an extensive and longitudinal description of clinical features [3] in a cohort of LSPD patients, who are rarely included in clinical studies. For the first time, we show that dysphagia predicts a worse outcome in these patients and some may still benefit from an increase in L-dopa [30, 31].

Unblinded clinical assessment is the main limitation of our study. However, our results are in line with ours [7, 8] and others' previous reports,[3, 4, 20, 21] giving consistency to our findings. The strength of our results should be

tempered by a possible underestimation of other factors of poor prognosis, due to the application of a multivariate analysis to a small sample of patients. Finally, there is a limitation regarding dysphagia assessment. Our study was not specifically designed to assess swallowing problems among LSPD patients, but to investigate overall clinical progression of these patients. For this reason, we investigated dysphagia by means of a subjective measure, i.e. the MDS-UPRDS, commonly used in clinical practice even if it can underestimate the problem [32] and we did not collect specific information on patients' diet and oral hygiene status. However, alternative objective and instrumental assessments of swallowing, such as fibre optic endoscopic evaluation of swallowing or videofluoroscopy, require patients' collaboration and are in-hospital procedures [33, 34], which was not applicable during in-home visits of demented and frail patients. Taken as a whole this highlights the possible underestimation of swallowing dysfunctions among our LSPD population and the need to perform dysphagia and nutrition-focused objective assessments among in LSPD.

Conclusion

LSPD is an orphan population expected to increase in the near future and responsible for a high caregiver burden. Their motor and non-motor disability is severe, and 20% is institutionalized. Nevertheless, clinical heterogeneity exists and the severity of axial signs and cognitive decline varies considerably. Consequently, even if disability milestones usually progress exponentially, a slower decline may also be possible. One-fifth dies after one year and the remaining become more disabled. Dysphagia severity

predicts a worse outcome, and attention should thus be taken to careful assessment and management of swallowing problems. On the other hand, L-dopa responsiveness seems to have no impact on prognosis in this late stage, although L-dopa maintains a slight effect on appendicular signs and especially in those cases with MCs, in whom the dose might be cautiously increased. Nevertheless, higher L-dopa dose will not improve swallowing and non-pharmacological interventions must be prioritized. Future pharmacological and non-pharmacological studies on LSPD patients should be mostly oriented to the management of dysphagia and other L-dopa unresponsive symptoms.

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Authors' Contributions

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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Conflict of interest and Financial Disclosures

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LEGEND FOR FIGURE

Figure 1. Kaplan-meier curves for the occurrence of the combined poor outcome (death/be institutionalized/HY 5) at follow-up for patients who are institutionalized (A), need a formal caregiver (B) or have a severe dysphagia (C) (MDS.UPDRS item 2.3 ≥ 2) at baseline;

LEGEND FOR TABLES

Table 1. Values are presented as mean (SD) if no otherwise specified. HY: Hoehn Yahr Stage; S&E: Schwab and England score; GDS: Geriatric Depression Scale (mild depression: 11- 20; severe depression: 21- 30); LEDD: levodopa equivalent daily dose; PDD: Parkinson's disease with dementia; BMI: Body mass index; MMSE: Mini Mental State Examination; EQ-5D VAS: Visual Analogue Scale of the Euro-QoL-5D; PDQ-8: PD questionnaire-8; NPI-12: Neuropsychiatric Inventory test 12-items; ZCBI: Zarit Caregiver Burden Inventory; LHS: London Handicap Scale; NMSS: Non motor symptoms scale; DDS: dopamine dysregulation syndrome; PEG: percutaneous endoscopic gastrostomy; Missing data: (*) → GDS 11/50 (22%) at baseline and 11/36 (30%) at follow-up; ED-5D VAS: 14/50 (28%) at baseline and 2/36 (5%) at follow-up; ^ Caregiver definition: 0= informal at home; 1= formal at home; nurses= 2; 3= not necessary/present; **This significance refers to the progression of MDS-UPDRS – I score of those patients assessed with MDS-UPDRS- I at follow-up (N = 36); the score worsened 0.7 points (± 4.0) corresponding to a 8.0% (± 24.3) increase. *** This significance refers to the progression of MDS-UPDRS – II score of those patients assessed with MDS-UPDRS- II at follow-up (N = 36); the score worsened 2.3 points (± 4.0) corresponding to a 6.0% (± 15.0) increase. **** This significance refers to the

progression of MDS-UPDRS – IV score of those patients assessed with MDS-UPDRS-IV at follow-up (N = 36); the score improved -1.5 points (± 3.8) corresponding to a 20% (± 54.8) increase.***** This significance refers to the progression of MDS-UPDRS – III MED ON score of those patients assessed with MDS-UPDRS- III at follow-up (N = 32); the score worsened 7.2 points (± 10.0) corresponding to a 15.7% (± 23.0) increase. NA: not available; ns: not significant. At MDS-UPDRS-I, NPI 12 item and NMSS a patient was considered as having a “positive” score for the item if score was ≥ 1 ; P values for baseline vs. follow-up questionnaires, and for ADPD vs. LSPD scores refer to mean values and not to number of affected patients.

Table 2. Multivariable Cox Proportional Hazards Model for time to death/be institutionalized/HY 5. HY: Hoehn Yahr Stage; S&E: Schwab and England score; PDD: Parkinson’s disease with dementia. AK: akinetic-rigid; NMSS: Non motor symptoms scale.

Table 3. L-dopa challenge test. Values are presented as mean (SD) if no otherwise specified. VAS-p: visual analogue scale for pain; VAS-f: visual analogue scale for fatigue; HY: Hoehn Yahr Stage; S&E: Schwab and England score; BP_supine: blood pressure in supine position; BP_orto: blood pressure after 3 minutes of standing; 1-OT: orthostatic hypotension; 1-OH: defined as decrease in systolic pressure >30 mmHg and in diastolic pressure >15 mmHg, within 3 minutes of standing; 2-OH: defines as decrease in systolic pressure >20 mmHg and in diastolic pressure >10 mmHg, within 3 minutes of standing. Missing data: (*) VAS-p and VAS-f 16/50; BP: 12/50;

Supplementary material

Table S1. Log-rank P values for time to “combined outcome” (death/be institutionalized/HY 5). PDD: Parkinson’s disease with dementia; AK: akinetic-rigid; TD: tremor-dominant; Moderate/severe dysphagia (MDS.UPDRS 2.3 item > 2).

ACCEPTED MANUSCRIPT

Patients data	LSPD (n= 50) Baseline	LSPD (n=36) 1 year follow-up	Baseline vs. 1 year follow-up
Age (yrs)	77.5 (5.9)	77.8 (7.2)	/
Education (yrs)	6 (5)	/	/
Women (n/total (%))	23/50 (46%)	17/36 (47%)	ns
BMI (Kg/m²)	22.8 (3.4)	22.3 (3.5)	<0.001
Age at disease onset (yrs)	62 (9.5)	/	/
Disease duration (yrs)	15.5 (6.5)	17 (6)	/
Levodopa treatment duration (yrs)	11.5 (8.9)	/	/
LEDD	1046 (388)	1033 (354)	ns
S&E (ON/OFF)	35.8 (12) / 30 (12)	28.6 (15.1)/NA	<0.001
HY (ON/OFF)	3.8 (0.9) / 4 (1)	3.7 (1.1) /NA	ns
LHS	0.3 (0.11)	0.28 (0.11)	<0.001
HY stage in ON (n (%))	2=8 (16%) 3=5 (10%) 4=24 (48%) 5=13 (26%)	2=6 16%) 3=6 (16%) 4=12 (33%) 5=12 (33%)	ns
Clinical phenotype (n (%))			/
Akinetic-Rigid	30 (60%)	22 (61%)	
Tremor dominant	15 (30%)	12 (33%)	
Mixed	5 (10%)	2 (5%)	
PDD (n (%))	34 (68%)	22 (61%)	ns
MMSE	21.4 (5)	19.7 (7.9)	<0.05
Psychosis (n (%))	28 (56%)	19 (53%)	<0.001
Neuroleptic treatment (n (%))	24 (48%)		
Urinary incontinence - % (MDS-UPDRS 1.10 > 2)	68%	80%	<0.01
Falls (n/month) - %	2 (4.4) – 50%	2 (5) – 55%	ns

Gait and walking aid			<0.001
Independent	5 (10%)	1 (3%)	
Cane	11 (22%)	10 (28%)	
Walker	11 (22%)	6 (17%)	
Another person	14 (28%)	8 (22%)	
Wheelchair-bound	9 (18%)	11 (30%)	
Nursing home	10 (20%)	8 (22%)	<0.05
Eating tasks independency	2.6±0.9	3±0.8	<0.001
MDS-UPDRS 2.4	58%	77%	
MDS-UPDRS 2.3 ≥2 - %			
Dysphagia severity			ns
MDS-UPDRS 2.3	1.6±1	1.7±1.2	
MDS-UPDRS 2.3 = 0- n, %	9 – 18%	9 – 25%	
MDS-UPDRS 2.3 = 1- n, %	12 – 24%	7 – 19%	
MDS-UPDRS 2.3 = 2 - n, %	18 – 36%	14 – 38%	
MDS-UPDRS 2.3 = 3 - n, %	11 – 22%	6 – 16%	
MDS-UPDRS 2.3 = 4 - n, %	0	2- 5%	
MDS-UPDRS 2.3 ≥2 - n, %	54%	61%	
MDS-UPDRS ≥3 - n, %	11 – 22%	8 – 22%	
PEG (n (%))	0	1 (2%)	
Caregiver ^	0 = 27 (54%) 1= 13 (26%) 2= 10 (10%)	0= 21 (58%) 1= 6 (16%) 2= 9 (25%)	ns
ZBDS	28.3 (13.3)	NA	/
Dead (n (%)), causes	/	10 (20%) pneumonia (n = 4); not determined (n = 4); intestinal cancer (n = 1); food asphyxiation (n = 1)	/
GDS*			
Depression (n (%))	15.6(4.5) *	14.5 (6.7)	ns
Light	34 (68%)	22 (61%)	ns
Severe	28 (56%) 6 (12%)	18 (50%) 4 (11%)	ns ns

MDS-UPDRS-I, total score Score, mean (SD) - n° of patients scoring positive in the item (%)	22.2 (7)	22.6 (6.7)	ns/ns**
Cognition	2.9 (1.2) – 92%	3.1 (1.5) – 94%	<0.01
Hallucinations & psychosis	1.4 (1.4) – 54%	1.3 (1.4) – 50%	ns
Depressed mood	1.9 (0.9) – 88%	2.2 (0.9) – 97%	ns
Anxious mood	1.5 (1.2) – 72%	1.8 (0.9) – 91%	ns
Apathy	1.8 (1.4) – 70%	1.9 (1.4) – 80%	ns
DDS	0.2 (0.5) – 16%	0.2 (1.4) – 2%	ns
Sleep problems	1.4 (1.2) – 68%	1.3 (1.2) – 77%	ns
Daytime sleepiness	1.6 (0.8) – 86%	1.1 (0.8) – 80%	<0.005
Pain	1.6 (1.2) – 74%	1.8 (1.1) – 86%	ns
Urinary problems	2.3 (1.1) – 94%	2.9 (1.1) – 94%	<0.001
Constipation problems	1.7 (1.3) – 74%	1.8 (1.1) – 83%	ns
Light headedness	1.2 (0.9) – 68%	0.7 (0.9) – 44%	<0.05
Fatigue	2.2 (1.2) – 84%	2.1 (0.8) – 91%	ns
MDS-UPDRS-II	35 (8.9)	36.0 (7)	0.05***
MDS-UPDRS-IV	4.6 (4.2)	3.6 (6.8)	<0.001****
MDS_UPDRS_III (OFF)	68.1 (14.1)	NA	/
MDS-UPDRS-III (ON)	56.4 (15.5)	58.5 (14.6)	<0.005*****
L-dopa induced Motor complications (n (%))	38 (76%)	24 (66%)	<0.01
Motor fluctuations (n (%))	32 (64%)	16 (44%)	<0.01
Troublesome motor fluctuations (n (%))	19 (38%)	11 (30%)	<0.01
Dyskinesias (n (%))	23 (46%)	20 (55%)	<0.01
Troublesome Dyskinesias (n (%))	11 (22%)	3 (8%)	<0.01
Painful off-dystonia (n (%))	16 (32%)	11 (30%)	ns
PDQ-8	60.4 (15)	62.1 (17.2)	ns
EQ-5D-VAS	43.7 (14.3) *	39.7 (15)*	<0.01
NMSS total score Score, mean (SD) - n° of patients scoring positive in the item (%)	118 (46.6)	128.6 (48.3)	<0.05
Cardiovascular	2.7 (3.4) – 61%	1.3 (1.7) – 47%	<0.05
Sleep/Fatigue	12.5 (7.2) – 100%	10 (7.5) – 100%	ns
Mood/Cognition	20.5 (7.2) – 96%	24.2 (18.4) – 97%	ns
Hallucination/perception	6.5 (8.2) – 58%	6.6 (8.6) – 52%	ns
Memory	20 (12.5) – 98%	22.1 (10.7) – 100%	<0.05
Gastrointestinal tract	10 (6.8) – 96%	8.8 (5.2) – 100%	ns

Urinary	17 (11.3) -94%	20.5 (12.9) – 97%	<0.001
Sexual function	20 (6.3) - 100%	23.3 (1.9) – 100%	<0.05
Miscellaneous	9.6 (5.4) 100%	11.5 (6.2)- 100%	<0.01
NPI-12 total score	21.7 (16.2)	23.1 (25.1)	ns
Score, mean (SD) - n° of patients scoring positive in the item (%)			
Delusion	1.3 (2.2) – 28%	1.5 (2.4) – 42%	<0.001
Hallucinations	2.5 (3.4) -52%	2.8 (3.8) – 50%	ns
Agitation/Aggression	1.9 (3) – 48%	1.5 (1.9) – 50%	ns
Depression	3 (1.9) – 88%	4.7 (3.1) – 97%	<0.001
Anxiety	2.5 (2.5) – 68%	3.4 (2.3) – 88%	ns
Elation/Euphoria	0.1 (0.6) – 6%	0.3 (2.1) – 5%	ns
Apathy/indifference	3.7 (3.7) – 70%	3.9 (4) – 72%	ns
Disinhibition	0.08 (0.3) – 6%	0.1 (0.7) – 2%	<0.001
Irritability/Lability	1.4 (2.3) – 52%	1.5 (1.9) – 50%	ns
Motor aberrant behaviour	1.7 (3) – 39%	2.2 (3.7) – 38%	ns
Sleep and Nighttime Behavior Disorders	4 (3.3) – 92%	2.4 (3.1) – 92%	ns
Appetite and Eating Disorders	1 (1.5) – 48%	1.1 (1.5)- 50%	ns

Table 1. Demographic and clinical characteristics of LSPD patients. Values are presented as mean (SD) if no otherwise specified. HY: Hoehn Yahr Stage; S&E: Schwab and England score; GDS: Geriatric Depression Scale (mild depression: 11- 20; severe depression: 21- 30); LEDD: levodopa equivalent daily dose; PDD: Parkinson's disease with dementia; BMI: Body mass index; MMSE: Mini Mental State Examination; EQ-5D VAS: Visual Analogue Scale of the Euro-Qol-5D; PDQ-8: PD questionnaire-8; NPI-12: Neuropsychiatric Inventory test 12-items; ZCBI: Zarit Caregiver Burden Inventory; LHS: London Handicap Scale; NMSS: Non motor symptoms scale; PEG: percutaneous endoscopic gastrostomy; DDS: dopamine dysregulation syndrome; Missing data: (*) → GDS 11/50 (22%) at baseline and 11/36 (30%) at follow-up; ED-5D VAS: 14/50 (28%) at baseline and 2/36 (5%) at follow-up; ^ Caregiver definition: 0= informal at home; 1= formal at home; nurses= 2; 3= not necessary/present; **This significance refers to the progression of MDS-UPDRS – I score of those patients assessed with MDS-UPDRS- I at follow-up (N = 36); the score worsened 0.7 points (± 4.0) corresponding to a 8.0% (± 24.3) increase. *** This significance refers to the progression of MDS-UPDRS – II score of those patients assessed with MDS-UPDRS- II at follow-up (N = 36); the score worsened 2.3 points (± 4.0) corresponding to a 6.0% (± 15.0) increase. **** This significance refers to the progression of MDS-UPDRS – IV score of those patients assessed with MDS-

UPDRS- IV at follow-up (N = 36); the score improved -1.5 points (± 3.8) corresponding to a 20% (± 54.8) increase.***** This significance refers to the progression of MDS-UPDRS – III MED ON score of those patients assessed with MDS-UPDRS- III at follow-up (N = 32); the score worsened 7.2 points (± 10.0) corresponding to a 15.7% (± 23.0) increase. NA: not available; ns: not significant. At MDS-UPDRS-I, NPI 12 item and NMSS a patient was considered as having a “positive” score for the item if score was ≥ 1 ; P values for baseline vs. follow-up questionnaires refer to mean values and not to number of affected patients.

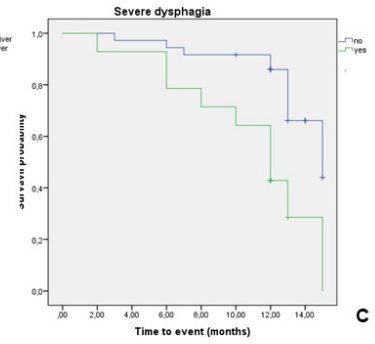
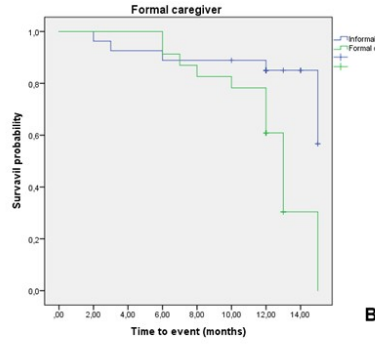
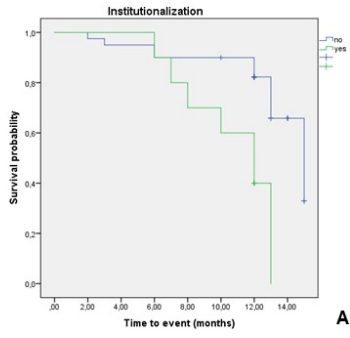
Variable	Hazard Ratio (95% CI)	P - value
Age	1.02 (0.93-1.11)	0.66
Gender	0.56 (0.18-1.73)	0.32
S&E (MED OFF)	0.95 (0.89 – 1.02)	0.21
HY (MED OFF)	0.91 (0.42- 1.95)	0.81
PDD	1.38 (0.23- 7.99)	0.71
NMSS total score	0.99 (0.99- 1.01)	0.59
MDS-UPDRS-item 2.3 (dysphagia)	2.2 (1.1- 4.2)	0.02

Table 2. Multivariable Cox Proportional Hazards Model for time to death/be institutionalized/HY 5.

HY: Hoehn Yahr Stage; S&E: Schwab and England score; PDD: Parkinson's disease with dementia. AK: akinetic-rigid; NMSS: Non motor symptoms scale.

LSPD patients (N= 50)			
	MED OFF	MED ON	p - value
MDS-UPDRS-III	68.1 (14.1)	58.4 (15.5)	< 0.001
Speech	2.5 (1.1)	2.5 (1.1)	0.1
Rigidity	9.7 (5)	6.5 (5)	< 0.001
Bradykinesia	34.5 (6)	31.5 (6)	< 0.001
Rest tremor	2,1 (2.8)	0.6 (1.3)	< 0.001
Arising from chair	3.3 (0.9)	3 (1)	0.001
Freezing of gait	2.6 (1.3)	2.4 (1.3)	0.05
Postural Stability	3 (0.9)	2.9 (0.9)	0.05
Posture	2.3 (0.8)	2.2 (0.8)	0.3
Gait	3.2 (0.9)	2.9 (0.9)	0.001
VAS-p	1.2 (2)*	0.3 (1.2)*	0.002
VAS-f	2.8 (3.2)*	2.8 (3.2)*	0.076
BP_supine	148/80 (31/14)	136/80 (26/17)	0.001/0.06
BP_ortho	142/81 (34/14)	121/75 (30/14)	< 0.001/ 0.002
1-OH (n (%))	9 (18%)	13 (26%)	0.001
2-OH (n (%))	13 (26%)	17 (34%)	0.05
AIMS	0.3 (1)	4 (7)	< 0.001
S&E	35.8 (12)	30 (12)	< 0.001
HY	4 (1)	3.8 (1)	0.0019
L-dopa dose (mg)	336 (102)		
Ocurrence of AEs	11 patients (22%) = drowsiness, 3 patients = symptomatic hypotension (6%), 2 patients (4%) = nausea/vomit		

Table 3. L-dopa challenge test. Values are presented as mean (SD) if no otherwise specified. VAS-p: visual analogue scale for pain; VAS-f: visual analogue scale for fatigue; HY: Hoehn Yahr Stage; S&E: Schwab and England score; BP_supine: blood pressure in clinostatic position; BP_orto: blood pressure after 3 minutes of standing; 1-OH: orthostatic hypotension; 1-OH: defined as decrease in systolic pressure >30 mmHg and in diastolic pressure >15 mmHg, within 3 minutes of standing; 2-OH: defines as decrease in systolic pressure >20 mmHg and in diastolic pressure >10 mmHg, within 3 minutes of standing. **Missing data:** (*) VAS-p and VAS-f 16/50; BP: 12/50;



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Highlights

- Late-stage Parkinson's disease patients have a high functional dependence;
- After one year, one-fifth dies and the remaining become more disabled;
- Dysphagia severity predicts a poor outcome (death, institutionalization, HY 5);
- L-dopa responsiveness seems to have no impact on prognosis;
- The management of dysphagia should be a priority of late disease stage.