The very late stage of Parkinson's disease: clinical characterization and disability determinants

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***OBJECTIVES**:* To analyze the characteristics of very late stage PD (≥35 years of disease) in a selected group of patients treated with subthalamic nucleus-DBS (STN-DBS), with the aim of describe the disease evolution and the factors associated with loss of independence and lower quality of life of long-surviving PD patient.

***METHODS**:* Five young-onset patients with average disease duration of 36.6 ± 2.2 years were enrolled. Neurological assessment included: Unified PD Rating Scale (UPDRS), Non-Motor Symptoms Scale and Questionnaire, Activities of Daily Living (ADL) scale, Instrumental ADL scale (IADL), Scale for Outcome in PD-Autonomic (SCOPA-AUT), electrophysiological study (including autonomic tests), neuropsychological tests and PD Questionnaire-39. The caregivers distress and the PD impact on their life were assessed by means of the Zarit Caregiver Burden Inventory (ZCBI).

***RESULTS**:* Age and DBS duration were 72.2 ± 5.2 and 14.5 ± 1.7 years.

Motor outcomes: All patients demonstrated a sustained motor response to dopaminergic treatment and STN-DBS, with average UPDRS-III improvement of 54.4% (Med-ON/Stim-ON vs Med-OFF/Stim-OFF). Moreover, all patients showed a sustained response in the motor complications scores, with the average dyskinesia duration and percentage of waking day spent in "OFF" (UPDRS item 32 and 39) still comprised between 0 and 25%. As expected, axial symptoms, and in particular speech impairment and postural instability, demonstrated a less marked response to medical and STN-DBS treatment (34.3%).
UPDRS-III scores, as well as axial subscores and the percentages of response to Ldopa and/or STN-DBS, did not correlate with quality of life and ADL scales.

Non-motor outcomes: All patients had constipation and hyposmia. Three patients reported urge-incontinence. RBD was present in 4 subjects, as well as speech impairment; 3 patients had drooling and mild dysphagia. Three subjects had orthostatic hypotension (2 symptomatic).
Higher NMSS/NMSQ/SCOPA-AUT scores strongly correlated with worse independence in ADL (ADL scale: ß: -0.765/-0.791/-0.740, *p= 0.054/0.064/0.072*; IADL scale: ß: -0.892/-0.890/-0.866, *p= 0.042/0.043/0.048*) and worse quality of life (PDQ-39: ß: 0.931/0.950/0.982, *p= 0.022/0.013/0.003*).

Neuropsychological outcomes: One patient was demented, one had a single- and one a multiple-domain PD-MCI. Three patients had a mild mood depression, while STAI revealed a significant state and trait anxiety scores in 2 patients. Apathy tests were altered in all patients.
The two patients with severe cognitive impairment (PD-D and multiple domain PD-MCI) showed higher ADL impairment (ADL/IADL scores: 2.5 ± 0.7/3.0 ± 1.4 vs. 5.3 ± 0.6/6.7 ± 1.5 [*p= 0.076/0.083*] and lower quality of life (PDQ-39: 58.8 ± 1.9 vs. 37.8 ± 17.2 [*p= 0.083*]).

Caregivers outcomes: Caregivers' evaluation revealed a moderate/severe distress (ZBI values > 40/88) in 2 spouses. Patients for whom caregiver reported greater distress had slightly higher UPDRS-III scores, worse non-motor scores and higher cognitive impairment.

***DISCUSSION*:** Despite the satisfactory control of motor features, all patients reported a significant amount of non-motor symptoms, confirming previous data on late-stage PD patients [1,2]; these symptoms were strongly associated with lower independence in ADL and worse quality of life. As expected [3], similar associations were observed in cognitive impaired patients.
Higher non-motor burden and cognitive impairment influenced also the caregiver's distress [1,4].

***CONCLUSIONS*:** To the best of our knowledge, this is the first comprehensive report of PD patients with disease duration of more than 35 years.
The sustained control of motor symptoms achieved with the advanced therapies, even after many years of PD, allows a better understanding of the disease evolution in its very advanced phases, demonstrating that the disability is mainly due to the progressive worsening of non-levodopa-responsive symptoms, non-motor symptoms and cognitive decline.

REFERENCES

1. *Coelho M et al. Dementia and severity of parkinsonism determines the handicap of patients in late-stage Parkinson's disease: the Barcelona-Lisbon cohort. Eur J Neurol 2015;22:305-12*
2. *Merola A et al. Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients. Brain 2011;134:2074-84*
3. *Lawson RA et al. Cognitive decline and quality of life in incident Parkinson's disease: The role of attention. Parkinsonism Relat Disord 2016;27:47-53*
4. *Martinez-Martin P et al. Burden, perceived health status, and mood among caregivers of Parkinson's disease patients. Mov Disord 2008;23:1673–80*