Movement Disorders
CLINICAL PRACTICE

Disability Milestones and Death in Parkinson's Disease under Subthalamic Neurostimulation

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With interest we read the article by Schnalke and colleagues who report long-term outcomes in their series of 162 patients with Parkinson's disease (PD) under deep brain stimulation (DBS) of the subthalamic nucleus (STN).[1] With a mean age at onset of 50 years and a mean disease duration at surgery of 11 years, their cohort compares well to published clinical trials and longitudinal cohorts of PD patients under DBS.[2,3] The authors focus on PD related disability milestones (that they chose to term "morbidity" milestones) by analyzing occurrence of recurrent falls, hallucinations, dementia, and institutionalization. These four milestones tend to cluster together in the late stages of PD and occur within approximately 5 years prior to death as reported by Kempster et al. in a landmark paper on a cohort of 129 pathologically proven PD cases.[4]

In the DBS cohort studied by Schnalke and colleagues it can be estimated from figure 3A that frequencies of individual milestones ranged within 25–50% at disease durations of ~15 years and ~4 years after DBS implantation (based on the demographic information given).[1] The authors compare occurrence of milestones to the historical Kempster cohort and find significantly longer milestone-free survival in their patients. Across the 39 patients that died at mean disease durations of 20 years, milestone(s) developed approximately 5 years before death (similar to the Kempster cohort). They conclude that in STN-DBS treated patients overall survival is long, most of which is spend with a favorable disability burden.

However, as the authors partly acknowledge, comparison with historical cohorts are problematic as DBS candidates represent a PD subgroup with younger age, fewer comorbidities, and without dementia or other disease milestones at surgery that are regarded as exclusion criteria for DBS. In an attempt to overcome this obstacle we previously analyzed our long-term series of 74 STN-DBS patients along with a retrospectively constructed control group of 61 PD patients without DBS similar in age at onset and baseline, sex distribution, and number of comorbidities.[5] Over a median observational period of 14 years DBS patients were at significantly lower risk of experiencing recurrent falls (hazard ratio = 0.57) and psychosis (hazard ratio = 0.26) in a Cox regression analysis adjusted for various potential baseline confounders. There was no difference in risk for dementia, institutionalization, or death. Over the follow-up period 27 DBS patients and 29 control patients died and we have now reanalyzed disease milestone occurrences in relation to time of death (Table 1). Apart from psychosis, which occurred more frequently in the control subgroup, milestone frequencies and intervals to death were not significantly different between the two subgroups with median durations for falls and psychosis of ~4–6 years and for dementia and institutionalization of ~3–4 years (Table 1).

Thus, our results support the findings of Schnalke and colleagues of the major disease milestones preceding death in STN-DBS patients along a temporal trajectory similar to that observed by Kempster and colleagues, suggesting that DBS has little influence on the progression of disability and death in the very late stage of PD. However, prior to this final disease stage, there are indeed signals from comparative studies, such as ours, suggesting that chronic subthalamic DBS may lower the risk for or delay some important disability milestones such as falls, psychosis, and need for long-term care and may be associated with slightly prolonged survival.[3,5] Reasons behind this may relate to the long-term control of motor complications and reductions in medication-induced side effects, which—together with more frequent contacts with medical teams—could lead to improved mobility, personal care, and general health, rather than to a true "disease-modifying" effect.[3]

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Table 1 *Disability milestone development prior to death in DBS treated and control PD patients*

	STN-DBS ($n = 27$)	Controls ($n = 29$)	*P*-Value
Baseline characteristics			
Female/male, *n*	9/18	10/19	0.93
Age at baseline, years	64.0 (58.6–69.0)	69.7 (64.4–71.3)	0.087
Age at onset, years	51.0 (41.4–55.0)	54.3 (47.5–59.0)	0.16
Disease duration, years	12.1 (8.4–17.8)	12.4 (8.2–22.3)	0.80
Number of comorbidities*	0 (0–0)	0 (0–1.0)	0.68
Milestones and death			
Disease duration at death, years	22.0 (16.4–28.5)	23.0 (15.3–26.5)	0.67
Time from baseline to death, years	8.6 (5.0–10.2)	8.5 (4.1–11.0)	0.72
Number of milestones developed until death	1 (1–3)	2 (1–3.5)	0.099
Time from first milestone to death, years	6.0 (3.4–8.2)	5.5 (3.6–10.0)	0.66
Developed recurrent falls, *n*	21	26	0.29
Time from recurrent falls to death, years	5.4 (3.4–8.2)	5.0 (2.1–8.9)	0.80
Developed psychosis, *n*	6	17	0.007
Time from psychosis to death, years	4.0 (2.4–7.1)	6.6 (4.3–8.9)	0.25
Developed dementia, *n*	10	14	0.43
Time from dementia to death, years	3.0 (1.7–4.3)	3.7 (2.8–8.1)	0.24
Required nursing home, *n*	8	8	0.99
Time from nursing home placement to death, years	2.7 (0.8–4.6)	4.1 (2.4–6.5)	0.43

Note: All patients from our long-term cohort that died during the observational period of ~14 years are included in this subgroup analysis. Ordinal and metric variables are given in medians (25th–75th percentile). For calculation of significance levels the chi-square test for categorical variables and the Mann–Whitney U test for metric variables were used.
Abbreviations: DBS, deep brain stimulation; STN, subthalamic nucleus.
*According to the Charlson comorbidity index.

Disclosure

Ethical Compliance Statement: The ethics committee of Innsbruck Medical University had approved this retrospective study, for which informed consent was not necessary. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Author Roles

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

P.M.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B.

W.E.: 2C, 3B.

W.P.: 1A, 2C, 3B. ■

References

1. Schnalke N, Konitsioti A, Frank A, et al. Morbidity milestones demonstrate long disability-free survival in Parkinson's disease patients with deep brain stimulation of the subthalamic nucleus. *Mov Disord Clin Pract* 2023; 10:569–578.
2. Deuschl G, Agid Y. Subthalamic neurostimulation for Parkinson's disease with early fluctuations: balancing the risks and benefits. *Lancet Neurol* 2013;12(1):25–1034.
3. Mahlknecht P, Foltynie T, Limousin P, Poewe W. How does deep brain stimulation change the course of Parkinson's disease? *Mov Disord* 2022;37: 1581–1592.
4. Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. *Brain* 2010;133:1755–1762.
5. Mahlknecht P, Peball M, Mair K, et al. Has deep brain stimulation changed the very long-term outcome of Parkinson's disease? A controlled longitudinal study. *Mov Disord Clin Pract* 2020;7:782–787.