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Short communication

Long-term follow-up of subthalamic nucleus deep brain stimulation in patients with Parkinson's disease: An analysis of survival and disability milestones

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ABSTRACT

Background: Data on the long-term survival and incidence of disability milestones after subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD) is limited.
Objectives: To estimate mortality and assess the frequency/time-to-development of disability milestones (falls, freezing, hallucinations, dementia, and institutionalization) among PD patients post STN-DBS.
Methods: A longitudinal retrospective study of patients undergoing STN-DBS. For mortality, Cox proportional hazards regression analysis was performed. For disease milestones, competing risk analyses were performed and cumulative incidence functions reported. The strength of association between baselines features and event occurrence was calculated based on adjusted hazard ratios.
Results: The overall mortality for the 109 patients was 16 % (62.1 ± 21.3 months after surgery). Falls (73 %) and freezing (47 %) were both the earliest (40.4 ± 25.4 and 39.6 ± 28.4 months, respectively) and most frequent milestones. Dementia (34 %) and hallucinations (32 %) soon followed (56.2 ± 21.2 and mean 60.0 ± 20.7 months after surgery, respectively). Higher ADL scores in the OFF state and higher age at surgery were associated with falls, freezing, dementia and institutionalization.
Conclusions: Long-term mortality rate is low after STN-DBS. Disease milestones occur later during the disease course, with motor milestones appearing first and at a higher frequency than cognitive ones.

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1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-recognized and effective treatment for patients with advanced Parkinson's Disease (PD) [1]. If motor complications (MC) and appendicular signs do significantly benefit from STN-DBS, axial signs such as gait, freezing-of-gait (FOG), postural instability and dysarthria are not as amenable to modulation [2,3]. In non-DBS cohorts, 81 %, 87 %, and 83 % of patients develop FOG, falls, dementia, hallucinations within 20 years of disease duration, respectively [4]. In DBS-cohorts the rates of disability milestones are similar, with 77 %, 61 %, 38 %, and 48 % of patients developing FOG, falls, dementia, psychosis [5]. These disability milestone tend to cluster together being strongly associated with disease progression [4,6,7]. A better characterization of the disability milestone development is needed in order to better inform the long-term prognosis and expectations of DBS.

The aim of this study was to characterize the long-term survival of PD patients undergoing STN-DBS surgery and to identify the frequency/time-to-occurrence of the disability milestones falls, FOG, hallucinations, dementia, and institutionalization.

2. Material & methods

This study has a longitudinal, retrospective design. All patients undergoing DBS-STN surgery between 2006 and 2012 and with a follow-up of at least 8 years have been included. DBS-GPI patients have been excluded from the study. PD was diagnosed according to the UK Brain Bank criteria [8] and selection criteria for DBS surgery mirrored the CAPSIT-protocol [9]. Patients who had the leads or the implanted pulse generator definitively removed during the follow-up were identified and censored at the time of system removal. At each post-operative visit, the presence of disability milestones was evaluated. Both falls and FOG were only considered if more than 6 months post surgery had elapsed. All data were retrospectively retrieved and analysed from baseline up to 8 years post-surgery. Patients were evaluated until the time of death or the end of the follow-up period (8 years), whichever occurred first.

Additional baseline pre-surgery features have been collected (Supplementary Table S1). These included the percentage of patients with significant gait impairment (≥2 on item 29 of the UPDRS-III) or postural instability (≥2 on item 30 of the UPDRS-III) in the OFF state. The c the clinical phenotype [postural instability/gait disorder (PIGD) or tremor dominant (TD)] [10], the levodopa-equivalent daily doses (LEDD) [11]. As our institution started using the MDS-UPDRS from 2012 onwards, the MDS-UPDRS II and III scores were inferred whenever only the UPDRS was available [12].

This study was approved by the Local Ethical Committee ("Comissão de Ética do Centro Académico de Medicina de Lisboa – CAML").

3. Data analysis

Clinical and demographic characteristics were presented as mean ± standard deviation or proportions, as appropriated. Two group comparisons (fallers vs non-fallers and freezers vs non-freezers) were performed using Mann-Whitney U tests for continuous variables or Chi-square tests for categorical ones. Multicollinearity was tested using Spearman coefficients between all possible pairs of variables (Supplementary Fig. S1).

For the primary outcome (i.e., death), Cox proportional hazards regression analysis was performed. The time-dependent survival was fit using each individual variable, and variables of interest were subsequently selected for adjustment and multivariable regression. The log-rank (Mantel-Cox) test was used for comparison of survival curves between groups and estimation of respective hazard ratios (Mantel-Haenszel). For secondary outcomes, the primary outcome (i.e., death) hindered the occurrence of secondary outcome in a time-dependent way. Thus, competing risk analyses were performed and cumulative incidences calculated for all secondary outcomes. Then, multivariable regression analysis in the presence of competing risks was performed using the semiparametric proportional hazards model (Gray's test). For all models, a backwards stepwise regression model was used. Analysis were performed using R 4.0.4.Exact p-values, hazard ratios and 95 % confident intervals are reported.

4. Data availability statement

Anonymized data of this study will be made available from the corresponding author upon reasonable request.

5. Results

5.1. Clinical and demographic baseline characteristics

One hundred and nine patients underwent STN-DBS during the study period (Table 1). During follow-up, 8 patients were censored: 7 due to system removal (on months 5, 35, 45, 57, 61, and 2 × 95) and 1 was referred to another institution (on month 72). Eighty-four patients reached the end of the follow-up [mean age 68.6 ± 7.6, mean disease duration 21.38 ± 4.38 years, mean Hoehn and Yahr (H&Y) 2.8 ± 1.1, mean LEDD 600.90 ± 370.14 mg (1252.66 ± 521.17 mg at baseline, average reduction of 49.64 ± 29.52 %, $p < 0.001$]. Stimulation parameters at the end of follow-up can be found on Supplementary Table S1.

5.2. Mortality

Seventeen patients died during the study (16 %). On average, patients died 62.1 ± 21.3 months after surgery (Fig. 1), at a mean age of 69.9 ± 6.0 years. Among patients who did die, falls preceded death by 34.6 ± 13.7 months, FOG by 35.8 ± 21.4 months, dementia by 18.5 ± 14.5 months and hallucinations by 18.7 ± 14.4 months. None of the dead was institutionalized. Age at surgery (HR 1.121, C.I. 1.035–1.463, $p = 0.019$) and the preoperative UPDRS part III score in the OFF state (HR 0.942, C.I. 0.890–0.996, $p = 0.037$) were significantly associated

Table 1
Demographic and clinic characteristics of study participants.

Gender: male, n = 109	55 (54.1 %)
Age at disease onset ($\bar{x}$ ± SD, n = 104)	47.9 ± 7.9
Age at surgery ($\bar{x}$ ± SD), n = 109	61.3 ± 7.5
Disease duration at surgery (y ± SD), n = 104	13.8 ± 5.5
UPDRS II OFF-MED ($\bar{x}$ ± SD), n = 98	25.7 ± 32.7
UPDRS II ON-MED ($\bar{x}$ ± SD), n = 98	8.9 ± 5.9
UPDRS III OFF-MED ($\bar{x}$ ± SD), n = 105	44.5 ± 13.4
UPDRS III ON-MED ($\bar{x}$ ± SD), n = 105	18.8 ± 17.6
UPDRS IV ($\bar{x}$ ± SD), n = 98	9.5 ± 4.9
MDS-UPDRS IV ($\bar{x}$ ± SD), n = 9	9.1 ± 5.3
H&Y OFF MED ($\bar{x}$ ± SD), n = 105	2.8 ± 0.2
H&Y ON MED ($\bar{x}$ ± SD), n = 105	2.0 ± 1.0
SE OFF ($\bar{x}$ ± SD), n = 100	51.9 ± 20.2
SE ON ($\bar{x}$ ± SD), n = 100	86.6 ± 14.9
Levodopa % response ($\bar{x}$ ± SD) n = 106	57.6 ± 13.5
LEDD mg ($\bar{x}$ ± SD), n = 107	1252.6 ± 521.2
Item 29 UPDRS III OFF ≥2, n = 105	65 (61.9 %)
Item 30 UPDRS III OFF ≥2, n = 105	43 (41.0 %)
Phenotype, n = 95	
Tremor	45 (47.4 %)
PIGD	39 (41.1 %)
Indeterminate	11 (11.6 %)
MMSE score ($\bar{x}$ ± SD), n = 100	27.8 ± 2.1
Neuropsychological diagnosis, n = 90	
Normal	71 (78.9 %)
Mild Cognitive impairment	19 (21.1 %)

Values are presented as mean ± SD. SE: Schwab and England ADL; LEDD: levodopa equivalent daily dose; PIGD: postural instability gait disorder; MMSE: mini mental state examination. UPDRS: Unified Parkinson Disease Rating Scale; MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale.

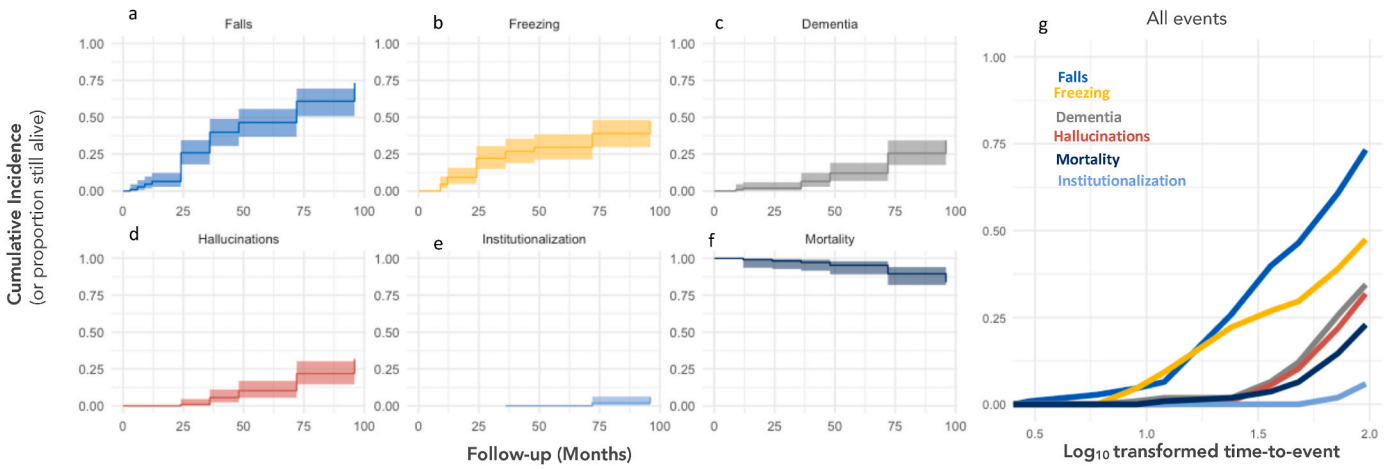

Fig. 1. Estimated cumulative incidence curves (a–e) for each milestone event with mortality treated as competing risk. Shaded areas represent (upper and lower) 95 % confidence intervals. Survival plots for the entire cohort (f) - Summary incidence plot across all events under study adjusted for competing risks (falls, freezing, hallucinations, dementia, mortality, and institutionalization). For the sake of visibility, values on the X-axis correspond to the base 10 logarithmic of the number of elapsed months to event (1 -> 10 months, 1.5 -> 32 months, 2 -> 100 months).(g).

with mortality (Supplementary Figs. S2 and S3).

5.3. Disability milestones

Falls were the most frequent event during the follow-up, with a competing risk-adjusted probability of 73 % at 8 years post-DBS (95 % C.I., 0.636–0.897). The average time from surgery to first fall occurrence was 40.4 ± 25.4 months. FOG was observed in 47 % (95 % C.I., 0.377–0.566) of the cohort, appearing on average after 39.6 ± 28.4 months. Hallucinations were reported for 32 % of the cohort (95 % C.I., 0.409–0.231), with an average time from surgery of 60.0 ± 20.7 months. Dementia developed in 34 % of patients (95%C.I., 0.254–0.436), with an average time from surgery of 56.2 ± 21.2 months. Institutionalization occurred for only 6 % of the patients (95 % C.I., 0.024–0.117), on average 62.3 ± 22.0 months after surgery (Fig. 1).

5.4. Disability milestones determinants

Compared to non-fallers, fallers had worse baseline scores in the UPDRS II and UPDRS III item 30 (postural instability) in the OFF state (**Supplementary Table S2**). Older age at surgery (HR 1.184, 95 % C.I., 0.779–1.086, $p = 0.004$) was significant associated with falls (Supplementary Figs. S2 and S3). Compared to non-freezers, freezers had significantly higher baseline scores in the UPDRS III item 29 (gait) in the OFF state (**Supplementary Table S3**). Older age at surgery (HR 1.186, 95 % C.I. 1.050–1.340, $p = 0.006$) and higher UPDRS part II score in the OFF state (HR 1.024, 95 % C.I., 1.012–1.040, $p = 0.000$) were significantly associated with freezing (Supplementary Figs. S2 and S3).

No baseline features under evaluation were found to be significantly associated with the development of hallucinations. In the case of dementia, both older age at surgery (HR 1.029, C.I. 1.000–1.374, $p = 0.05$) and preoperatory UPDRS part II score in the OFF (HR 1.026, C.I. 1.014–1.037, $p = 0.000$) and ON states (HR 0.996, C.I. 0.711–0.962, $p = 0.014$) were significantly associated with its development. For institutionalization, both preoperatory the UPDRS part II score in the OFF state (HR 1.010, 95 % C.I., 1.010–1.020, $p = 0.000$) and older age at surgery (HR 1.190, C.I. 1.070–1.320, $p = 0.001$) were significantly associated with it (Supplementary Figs. S2 and S3).

6. Discussion

Reflecting high heterogeneity of study populations in regard to disease and follow-up duration, highly variable mortality rates have been reported in long-term DBS cohorts (17–61 %) [2,13,14]. We report figures for cumulative mortality that are similar to a previous study (17 % in both cohorts) [15]. The cumulative incidence of disability milestones was also in line to what was previous described in other cohorts with similar follow-up times (falls 73 %, freezing 47 %, hallucinations 32 %, dementia 34 % and institutionalization 6 %) [14,16]. In all these studies, age and disease duration at surgery were similar to our cohort. The importance of comparing cohorts with similar demographic characteristics is reinforced by the increase in mortality rates with older age at surgery.[15,16]Older age at PD onset has been reported as significantly associated with increased mortality. However, findings from Kempster et al. have instead suggested that death (and disability milestones) occur at around the same age regardless of the age at PD onset [7,17]. In our cohort, the mean age of death is similar to what has been previously observed despite the longer disease duration (69.9 ± 6.0 in our cohort vs 75.5±9.1[7]). Thus, mortality would be related to chronological age more than to disease duration, or age of disease-onset.

Regarding the milestone-to-death interval, we have found a similar temporal relationship as previous studies [7], with falls preceding death by 34.6 ± 13.7 months, FOG by 35.8 ± 21.4, dementia and hallucinations by 18.5 ± 14.5 and 18.7 ± 14.4, respectively. The observed juxtaposition between the order of milestone event occurrence herein observed and that reported in previous studies despite fundamentally different cohort characteristics (e.g DBS status) suggests it to follow a somewhat stereotyped pattern that may not be as amenable to modulation by current practices (Fig. 1).

Falls and FOG were both the earliest and the most frequent disability milestones, tending to occur at around the same time. In previous studies, falls and FOG had developed in ~60 % of patient 7–8 years into the follow-up. Not surprisingly, this axial sign deterioration occurs in a time-dependent fashion, occurring at a lower incidence in cohorts of shorter disease duration at surgery and shorter follow-up periods [2,3,16]. Older age at STN-DBS was significantly associated with the development of both falls and freezing. In turn, higher baseline UPDRS II in the OFF state was significantly associated with freezing but not falls. Our results reinforce the previously highlighted importance of baseline disease severity, namely in OFF, for future incidence of axial disability milestones, irrespectively of levodopa responsiveness. FOG is not classically regarded as a disability milestone but the response of FOG to DBS-STN has been controversial and, as such, there is a need for future systematic studies.

Cognitive/behavioural milestones had an incidence lower than that of axial symptoms. As for the aforementioned events, the development

of hallucinations and dementia after STN-DBS has been highly variable, ranging from 18 to 61 % for hallucinations [5,13,14], and from 5 to 61 % for dementia [13,14].

Institutionalization occurred very seldom in the present study (as opposed to other DBS [14,16] and non-DBS cohorts [18]), an observation not surprising and in line with a previous Portuguese on late-stage patients [18]. In all likelihood, sociocultural and socioeconomic factors explain in its entirety to observed extremely low institutionalization rates.

The present study lacks a control group, but comparing the observed numbers with comparable size historical cohorts [4,19], one might conclude that STN-DBS patients develop the same disability milestones as non-DBS PD patients, but albeit at a lower rate despite similar disease duration [4,19]. Age at PD onset may be a possible reason for the divergence, with DBS patients being relatively younger at disease onset and at the end of follow-ups [4,19]. Accordingly, a negative correlation between age at disease onset and time-to-development of the first disease milestone has been previously reported [6,7]. Compared to the Sydney cohort, a delay of 10–15 years in achieving the same level of disability milestones was found in the Toronto study [16]. Younger age of onset in the Toronto study was the explanation put forward for the difference, suggesting that the disease progresses slower in younger patients but that disability milestones are reached at a similar age independently of age at onset [7,16,17]. Interestingly, even if MC may be well attenuated with STN-DBS, surgery was herein observed not to prevent/delay its development. Of note, a decrease in dopaminergic medication after surgery and the lack of cognitive impairment before DBS may together explain why falls developed before hallucinations (in contrast to the usual sequence of events) [6,7,14].

7. Strength and limitations

The present study is one of the largest long-term cohort of STN-DBS PD patients monitoring incidence rates and baseline predictors of PD disability milestones. The authors recognize the existence of missing data, mostly at the level of the pre-surgery assessment in variables pertaining to the neuropsychological evaluation (MMSE scores lacking for 8 % of the cohort, final neuropsychological diagnosis lacking for 17 % of all). Nonetheless, for all main/secondary outcomes (i.e., survival and prevalence/incidence of disability milestones) no missing data was present. The present study has a retrospective design and like most long term DBS follow-up studies, lacks a control group. To minimize this limitation, data was discussed using historical DBS and non-DBS cohorts.

8. Conclusions

Long-term mortality rate is low after STN-DBS. Disease milestones occur later during the disease course, with motor milestones appearing first and at a higher frequency than cognitive ones. Given the strong association between age (but not disease duration) and mortality/milestone development, the present data supports STN-DBS to be performed earlier rather than later.

Authors contribution

RB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing-original draft preparation, Writing – Review & Editing; LCG: Data curation, Writing – Review & Editing; MBC: Data curation, Writing – Review & Editing; PPL: Data curation, Writing – Review & Editing; ACC: Data curation, Writing – Review & Editing; MF: Conceptualization, Methodology, Data curation, Writing – Review & Editing; PB: Data curation, Formal Analysis, Investigation, Methodology, Software, Writing-original draft preparation, Writing – Review & Editing; AV: Data curation, Writing – Review & Editing; HC: Data curation, Writing – Review & Editing; LA: Data curation, Writing – Review & Editing; SR: Data curation, Writing – Review & Editing; A GF: Data curation, Writing – Review & Editing; JJF: Data curation, Writing – Review & Editing; MMR: Data curation, Writing – Review & Editing; MC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing-original draft preparation, Writing – Review & Editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105921.

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