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Parkinson's disease progression at 30 years: a study of subthalamic deep brain-stimulated patients

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Summary

Clinical findings in Parkinson's disease suggest that most patients progressively develop disabling non-levodopa-responsive symptoms during the course of the disease. Nevertheless, several heterogeneous factors, such as clinical phenotype, age at onset and genetic aspects may influence the long-term clinical picture. In order to investigate the main features of long-term Parkinson's disease progression, we studied a cohort of 19 subjects treated with subthalamic nucleus deep brain stimulation after >20 years of disease, reporting clinical and neuropsychological data up to a mean of 30 years from disease onset. This group of patients was characterized by an early onset of disease, with a mean age of 38.63 years at Parkinson's disease onset, which was significantly lower than in the other long-term subthalamic nucleus deep brain stimulation follow-up cohorts reported in the literature. All subjects were regularly evaluated by a complete Unified Parkinson's Disease Rating Scale, a battery of neuropsychological tests and a clinical interview, intended to assess the rate of non-levodopa-responsive symptom progression. Clinical data were available for all patients at presurgical baseline and at 1, 3 and 5 years from the subthalamic nucleus deep brain stimulation surgical procedure, while follow-up data after >7 years were additionally reported in a subgroup of 14 patients. The clinical and neuropsychological performance progressively worsened during the course of follow-up; 64% of patients gradually developed falls, 86% dysphagia, 57% urinary incontinence and 43% dementia. A progressive worsening of motor symptoms was observed both in 'medication-ON' condition and in 'stimulation-ON' condition, with a parallel reduction in the synergistic effect of 'medication-ON/stimulation-ON' condition. Neuropsychological data also showed a gradual decline in the performances of all main cognitive domains, with an initial involvement of executive functions, followed by the impairment of language, reasoning and memory. Thirty years after the disease onset, most patients presented non-levodopa-responsive symptoms, although the effect of both subthalamic nucleus deep brain stimulation and dopaminergic therapies still showed significant efficacy on the main disease cardinal features. Nevertheless, compared with other subthalamic nucleus deep brain stimulation follow-up studies, which included patients with a shorter disease duration at the time of surgery, a higher prevalence of axial and non-levodopa-responsive symptoms was observed in the long-term evaluations, confirming that several complex aspects underlie the development of non-motor symptoms and other features of Parkinson's disease progression, even in patients with an early disease onset and a prior long-lasting response to dopaminergic therapies.

Key words: Parkinson's disease; motor complications***;*** DBS***;*** longitudinal***;*** levodopa***;*** subthalamic nucleus

Abbreviations: DBS = deep brain stimulation; UPDRS = Unified Parkinson's disease rating scale

Introduction

Parkinson's disease is a common neurodegenerative disorder, clinically characterized by the progressive impairment of several motor and non-motor neurological functions (Lees et al., 2009). Zetusky and colleagues (1985) initially suggested, and the results of the DATATOP study (Jankovic et al., 1990) later confirmed, that different Parkinson's disease clinical phenotypes might have different prognosis, with worse clinical outcomes in patients with bradykinesia, rigidity, postural instability and gait disturbances and a milder disease course in patients with tremor dominant clinical features.

Clinicopathological studies examined the amount of biochemical alterations in autoptic brains of patients with Parkinson's disease, reporting that tremor dominant clinical phenotype was associated to the lowest extent of neuropathological alterations (Rajput et al., 2008, 2009), the longest disease duration and the greatest delay in the onset of falls and cognitive decline (Selikhova et al., 2009). Moreover, Kempster et al. (2007) investigated the relationship between age at Parkinson's disease onset, heterogeneity in the patterns of response to dopaminergic therapies and Parkinson's disease clinical course, observing that younger patients with more severe motor fluctuations showed a slower disease evolution than older non-fluctuating patients, even if both groups reached similar clinical endpoints at a similar age. In addition, genetic factors were also correlated to Parkinson's disease clinical course; mutations in the LRRK2 gene were identified as the most common genetic determinant of Parkinson's disease (Klein and Lohmann-Hedrich, 2007), Parkin gene mutations were found in ∼9–20% of patients with early onset Parkinson's disease and a further 1% of cases were related to mutations in PINK1 and DJ-1 (Lucking et al., 2000; Klein et al., 2005; Hardy et al., 2009).

Overall, numerous data suggest that Parkinson's disease clinical evolution might be heterogeneous, although a very limited number of studies report data on the clinical progression after 10 years since onset of the disease (Marras et al., 2005; Hauser et al., 2007; Diem-Zangerl et al., 2009) and the exact relevance of the different prognostic factors is still a matter of debate (Marras et al., 2002; Post et al., 2007). At the present time, the most comprehensive data on the long-term Parkinson's disease clinical course comes from the Sydney Multicentre Study (Hely et al., 1999, 2005, 2008); in this cohort of patients followed for an extended time after disease onset, an elevated mortality rate was found after 10 years (Hely et al., 1999), a predominance of autonomic disturbances, falls, neuropsychiatric symptoms and dementia at 15 years (Hely et al., 2005), and finally, a severe impairment of cognitive function at 20 years (Hely et al., 2008). Overall, the results of the Sydney Multicentre Study suggest that the majority of patients with Parkinson's disease will develop disabling non-levodopa-responsive symptoms during the course of the disease. Nevertheless, there are no clinical data describing the Parkinson's disease progression after >20 years from disease onset.

The aim of our study was to report the main clinical features of Parkinson's disease progression in a selected group of patients, characterized by a long-term preserved response to dopaminergic therapies. For this purpose, we assessed the clinical and neuropsychological evolution of a cohort of 19 patients, treated with subthalamic nucleus deep brain stimulation (DBS) after an average of 22.84 years of disease, and followed prospectively up to 30 years from the onset of Parkinson's disease.

This cohort included patients significantly younger than those in the other main long-term follow-up studies: the mean age at Parkinson's disease onset was 38.63 years old, in comparison with the mean 54 years of age of the patients in the Sydney Multicentre Study reaching the 20 years of clinical observation

(Hely et al., 2008), the 56 years of age of the same cohort examined at 15 years (Hely et al., 2005) and the 62 years of age of the cohort initially enrolled in the study (Hely et al., 1999).

Materials and methods

We reported the clinical and neuropsychological data, up to a mean of 30 years of disease (mean disease duration: 30.76 ± 2.24 years), of 19 patients with Parkinson's disease who underwent subthalamic nucleus DBS after 22.84 ± 2.29 years of disease. The selection criteria of the Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (CAPSIT-Parkinson's disease) (Defer et al., 1999) were met by all subjects at the time of surgery. The baseline presurgical assessment was compared to the clinical and neuropsychological evaluations obtained after 1 year (mean disease duration: 23.92 ± 2.35 years), 3 years (mean disease duration: 25.72 ± 2.31 years) and 5 years (mean disease duration: 28.15 ± 1.93 years); an additional evaluation after >7 years from subthalamic nucleus DBS was also carried out on 14 subjects, at a mean follow-up duration of 8.42 years (range: 7.5–11.33) and at a mean disease duration of 31.27 ± 2.34 years.

Kaplan–Meier survival analyses were performed to estimate the median disease duration after the development of the main axial, non-motor and psychiatric symptoms and to determine whether the survival distribution of these symptoms might be influenced by gender, Parkinson's disease clinical feature (akinetic-rigid versus tremor dominant) and age at Parkinson's disease onset (younger than 40 years old versus patients aged 40–49). Informed consent was given by all the subjects.

Clinical and demographic characteristics

The study included all patients treated with subthalamic nucleus DBS at our Centre after >20 years of disease duration; based on this criterion, 19 out of the 129 patients with Parkinson's disease treated by subthalamic nucleus DBS between 1998 and 2006 were selected.

The main demographic characteristics are summarized in Table 1. The cohort consisted of nine males and 10 females treated with subthalamic nucleus DBS following the surgical procedure previously described elsewhere (Lanotte et al., 2002); Parkinson's disease onset was before age 30 in two patients, between 30–40 in eight patients and between 40–50 years of age in the remaining nine patients. Tremor was the presenting symptom in eight patients, while the onset was characterized by bradykinesia and rigidity in the others.

Table 1 Clinical and demographic data at subthalamic nucleus DBS and at last follow-up evaluation

Clinical/demographic characteristics	Cohort (19 patients)
Gender (male/female)	9/10
Age at Parkinson's disease onset, MD ± SD (range) (years)	38.63 ± 6.27 (26–49)
Age at subthalamic nucleus DBS, MD ± SD (range) (years)	61.47 ± 5.73 (50–69)
Disease duration at subthalamic nucleus DBS, MD ± SD (range) (years)	22.84 ± 2.29 (20–28)
Age at last follow-up, MD ± SD (range) (years)	69.39 ± 5.79 (57–78)
Disease duration at last follow-up, MD ± SD (range) (years)	30.76 ± 2.24 (27.7–36.3)
Mean follow-up duration, MD ± SD (range) (years)	7.92 ± 1.89 (5.1–11.3)

Clinical assessment

A complete Unified Parkinson's disease rating scale (UPDRS) (Fahn et al., 1987) evaluation was carried out at baseline (before subthalamic nucleus DBS), both in the 'OFF' condition (at least 12 h after the last levodopa dose) and in the 'ON' condition (40 min after the administration of a levodopa challenge dose, consisting of 1.5× the normal morning dose). Following the CAPSIT-Parkinson's disease protocol (Defer et al., 1999), the same evaluation was performed at follow-up in the four possible conditions: stimulation ON/medication OFF; stimulation OFF/medication OFF; stimulation OFF/medication ON; stimulation ON/medication ON. The clinical data listed in Table 3 were collected by means of UPDRS and a clinical interview, paying particular attention to the main axial, non-motor and psychiatric symptoms: the patients were assessed for falls (score ≥ 2 on item 13 of UPDRS), postural instability (score ≥ 2 on item 30), non-levodopa-responsive freezing of gait (score ≥ 2 on item 14 of UPDRS in 'ON' condition), urinary incontinence (need to use a diaper or a catheter), dysphagia (score ≥ 2 on item 7) and speech difficulties (score ≥ 2 on item 18). For constipation, postural hypotension, mood depression and hallucinations, we considered the need of pharmacological treatment as the most consistent indicator of the patient's functional state.

Neuropsychological assessment

All patients underwent a standardized battery of cognitive tests, assessing reasoning (Raven Colour Matrices), memory (Bisyllabic Words Repetition test, Corsi's Block Tapping test and Paired Associate Learning), language (category verbal fluency) and frontal executive functions (Trail Making Test part B, Phonemic Verbal fluency and Nelson Modified Card Sorting test). In order to obtain comparable categorical data, we defined a 0–2 score for each test (0 = normal, 1 = moderate impairment, 2 = severe impairment) and then calculated a cognitive index for each cognitive domain, corresponding to the sum of the related subtests (Aybek et al., 2007). Dementia was defined by the impairment in two or more cognitive domains [Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR); American Psychiatric Association, 2000], while patients who obtained a score below the cognitive index in only one cognitive domain were diagnosed as having a moderate cognitive impairment. Mood was evaluated by means of the Beck Depression Inventory (BDI), a 21-item self-rated scale. The total score was obtained considering all items, rated from 0 to 3; scores from 0 to 9 indicate absence of depression, from 10 to 17 mild depression, from 18 to 24 moderate depression, and, finally, scores >25 are indicative of severe depression.

Statistical analysis

Descriptive statistics (mean, standard deviation and range) were used for continuous variables, while categorical variables were described as percentages of subjects falling in each group. The main UPDRS sections scores were compared by means of the non-parametric Friedmann rank sum test and when appropriate, by the Wilcoxon rank sum test, at different timelines (baseline, 1, 3, 5 and >7 years). Cochrane Q-test was used for categorical variables. The median disease duration at the development of the main axial, non-motor and neuropsychiatric symptoms was estimated by means of Kaplan–Meier survival analyses. Time to event was censored at the end of follow-up and differences in the estimated survival distribution by gender, Parkinson's disease clinical feature (akinetic-rigid versus tremor dominant) and age at onset (younger than 40 years old versus 40 years old or older) were examined using the log rank test. All P-values reported are two-tailed and a $P < 0.05$ was considered statistically significant. The analyses were performed using PASWStat 18 for Windows.

Results

Motor symptoms, complications of therapies and activities of daily living

As shown in Fig. 1, the long-term follow-up evaluation revealed a progressive worsening of UPDRS-III motor score in medication 'ON' conditions, with a UPDRS-III 'stimulation OFF/medication ON' mean score that varied from a baseline value of 22.77 to 38.61 at 5 years ($P = 0.001$) and a last follow-up value of 39.20 ($P < 0.001$). A similar worsening was also observed for the 'stimulation ON' condition, with a 'stimulation ON/medication OFF' UPDRS-III mean score that progressively increased from the first year value of 29.97 to 37.28 at 5 years ($P = 0.006$) and to the last follow-up value of 38.10 ($P = 0.002$). The synergistic effect of subthalamic nucleus DBS and dopaminergic therapies (stimulation ON/medication ON condition) showed a parallel decline, ranging from the first year mean value of 18.25 to 26.38 at 5 years ($P = 0.018$) and to the last follow-up value of 27.57 ($P < 0.001$). On the contrary, UPDRS-III 'medication OFF' and 'stimulation OFF' motor score did not change significantly between baseline and the last evaluation (from 61.40 to 63.23; $P = 0.847$).

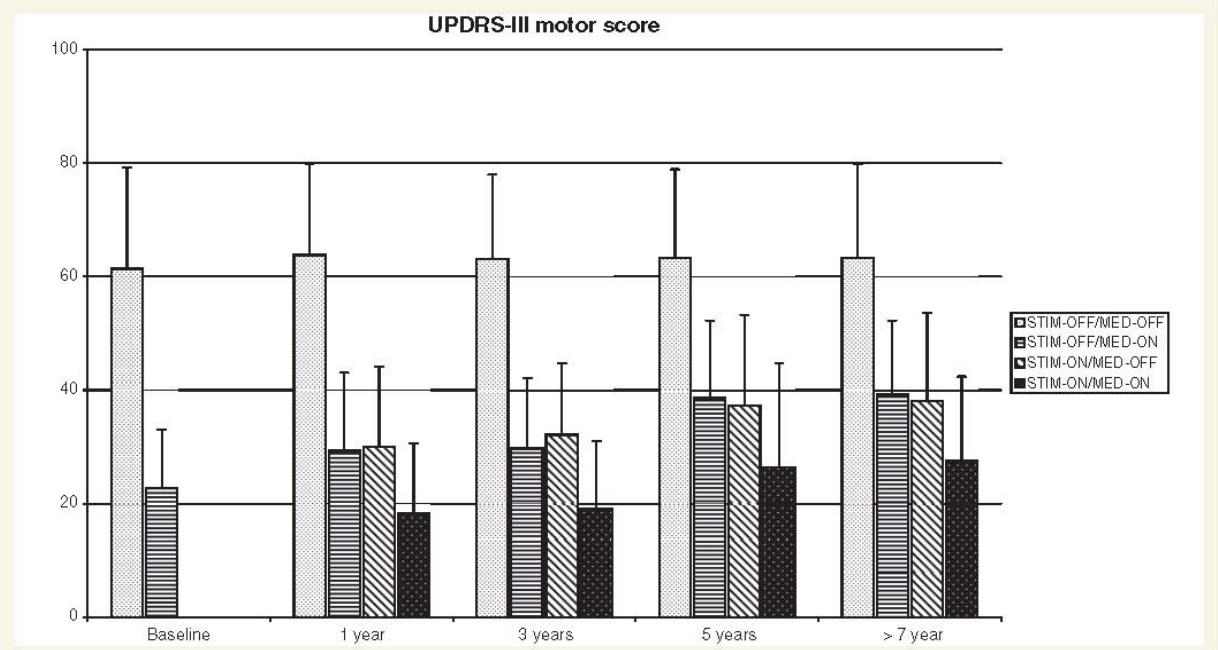

Figure 1 Evolution of the different UPDRS-III motor score CAPSIT-Parkinson's disease conditions at different time points from surgery.

According to the data reported in Table 2, complications of therapy (UPDRS-IV) significantly improved after neurosurgical treatment ($P < 0.001$). However, the global improvement initially achieved by subthalamic nucleus DBS, gradually decreased in the following years, with a progressive rise of UPDRS-IV mean score at 3 years ($P = 0.254$), 5 years ($P = 0.174$) and at >7 years ($P = 0.044$). Activities of daily living score showed a similar evolution: UPDRS-II medication 'OFF' mean score initially improved ($P < 0.001$) at the first year evaluation, to successively rise at 3 years ($P = 0.09$), 5 years ($P = 0.07$) and at >7 years ($P = 0.007$). UPDRS-II medication 'ON' mean scores did not change significantly between baseline, 1 and 3 years of follow-up ($P = 0.51$), while it showed a slight increase at 5 years ($P = 0.292$) and a significant worsening at the last evaluation ($P = 0.01$). Finally, Schwab and England scale medication 'ON' mean scores, which provide a global evaluation of the activities of daily living, remained stable between baseline, 1 ($P = 0.54$) and 3 years of follow-up ($P = 0.49$), while it significantly declined at 5 years ($P = 0.002$) and at >7 years ($P < 0.001$). The mean levodopa equivalent daily dose values decreased in the first year from surgery (Table 3), ranging from a mean of 890.3 mg/day to 336.5 mg/day, while in the course of the successive evaluations the levodopa

equivalent daily dose slightly increased to 381.6 mg/day at 3 years, 488.9 mg/day at 5 years and 435.1 mg/day at >7 years.

Table 2 Mean ± SD (range) scores of UPDRS sections I, II, IV, V and VI (Schwab and England scale) at different follow-up durations

	Baseline	1 year after STN DBS	3 years after STN DBS	5 years after STN DBS	>7 years after STN DBS
UPDRS-I	1.90 ± 1.80 (0–5.5)	2.25 ± 2.1 (0–7)	3.40 ± 2.77 (0–5)	3.93 ± 3.31 (0–9.5)	4.58 ± 2.44 (2–9.5)
UPDRS-II					
Score in 'OFF'	28.80 ± 5.9 (17.5–37)	13.825 ± 6.57 (2–26)	16.41 ± 7.41 (6–34)	18.00 ± 10.25 (6–36)	20.35 ± 8.32 (11.5–36)
Score in 'ON'	12.05 ± 5.37 (5–29)	11.37 ± 5.90 (0–25)	13.65 ± 8.42 (6–38)	15.80 ± 10.43 (6–38.5)	17.18 ± 6.72 (7.5–38.5)
UPDRS-IV	10.15 ± 3.10 (3–16)	1.75 ± 2.06 (0–7)	2.92 ± 3.17 (0–10)	4.07 ± 3.52 (1–10)	5.23 ± 2.95 (1–11)
UPDRS-V score in "ON" (%)	2.57 ± 0.37 (2–3)	2.50 ± 0.70 (2–4)	2.70 ± 1.00 (2–5)	3.17 ± 0.95 (2.5–5)	3.22 ± 0.57 (3–5)
UPDRS-VI score in "ON" (%)	81.25 ± 10.74 (70–100)	83.68 ± 14.22 (60–100)	82.00 ± 18.6 (30–100)	70.83 ± 19.75 (30–90)	69.20 ± 18 (30–90)

A score of 100% at the Schwab and England scale (UPDRS section VI) indicates a normal functioning in activities of daily living, while 70% indicates some loss of independence. STN = subthalamic nucleus.

Falls, postural instability and freezing of gait

According to the data reported in Table 3, few patients experienced falls at baseline and after 1 year of follow-up, while this percentage showed a slight increase at 3 years ($P = 0.368$) and a sharp rise at 5 ($P = 0.001$) and >7 years ($P < 0.001$). However, a steeper progression was observed in postural instability, which gradually increased from the first year ($P = 0.025$), reaching a prevalence value of 89% at 5 years ($P < 0.001$) and 100% at >7 years ($P < 0.001$). Moreover, the rate of patients with non-levodopa-responsive freezing of gait significantly increased at 5 years ($P = 0.003$) and at >7 years ($P < 0.001$). Time to event survival curves (Fig. 2) showed that most patients developed a global impairment of gait after ~25 years from the onset of Parkinson's disease. Postural instability seemed to be the most precocious event, occurring after a median disease duration of 26.1 years of disease (95% CI: 23.1–29.97 years), followed by falls and non-levodopa-responsive freezing of gait, which occurred after a median disease duration of 30.22 years (95% CI: 27.8–32.5 years) and 30.5 years (95% CI: 29.64–31.35 years), respectively. Patients with tremor-dominant Parkinson's disease feature and patients younger than 40 years old at the disease onset showed a lower probability to develop non-levodopa-reponsive freezing of gait ($P < 0.05$), while no significant correlations were observed for falls and postural instability.

Dysphagia and speech difficulties

At baseline, a moderate dysphagia was present in only one patient, who had undergone subthalamic nucleus DBS after 21 years of Parkinson's disease (Table 3). However, during the course of follow-up, the prevalence of dysphagia significantly increased at 3 ($P = 0.015$), 5 ($P < 0.001$) and >7 years ($P < 0.001$), and in three cases a percutaneous gastrostomy was required. Speech difficulties significantly worsened after 5 years from surgery ($P = 0.003$), and a further decline was observed in patients reaching a follow-up observation longer than 7 years ($P = 0.001$). The time to event survival curves reported in Fig. 3 showed that speech difficulties and dysphagia had a similar progression; the median duration of disease at the time of onset was 30.33 years (95% CI: 28.1–32.6 years) for dysphagia and 29.16 years (95% CI: 26.57–31.54) for speech difficulties, while the three patients who had undergone percutaneous gastronomy were affected by Parkinson's disease for more than 30 years. The survival distributions for these symptoms were not influenced by gender, Parkinson's disease clinical feature and age at Parkinson's disease onset.

Constipation, postural hypotension and urinary incontinence

The rate of patients requiring pharmacological treatment for constipation and postural hypotension rose significantly from baseline to last follow-up evaluation (Table 3). No patient needed pharmacological treatment for postural hypotension at baseline and only one subject used midodrine after 1 and 3 years of follow-up ($P = 0.368$). However, at >7 years from surgery, midodrine or fludrocortisone were prescribed to a significantly higher percentage of patients ($P = 0.01$). A similar trend was observed for constipation and urinary incontinence: the prevalence of patients requiring pharmacological treatment for constipation significantly rose at 5 years ($P = 0.007$) and at >7 years ($P = 0.002$), while a catheter or a diaper became necessary for ~20% of subjects at 3 years ($P = 0.018$), 37% at 5 years ($P = 0.001$) and >50% at >7 years ($P < 0.001$). The time to event survival curves reported in Fig. 4 showed that the prevalence of these symptoms increased dramatically after 30 years of disease: the median duration of disease at the time of onset was 30.33 years for urinary incontinence (95% CI: 29.5–31.2 years), 30.83 years for constipation (95% CI: 30.6–31 years) and 33.5 years for postural hypotension (95% CI: 31.5–35.5 years). Gender, Parkinson's disease clinical feature and age at the Parkinson's disease onset did not show a significant influence on survival distribution of these symptoms.

Table 3 Percentages of patients showing non-levodopa-responsive symptoms at different follow-up duration

	Baseline (%)	1 year after STN DBS (%)	3 years after STN DBS (%)	5 years after STN DBS (%)	>7 Years after STN DBS (%)
Falls	3/19 (16)	3/19 (16)	4/19 (21)	9/19 (47) [*12/19 (63)]	9/14 (64)
Postural instability	3/19 (16)	8/19 (42)	9/19 (47)	17/19 (89) [*18/19 (95)]	14/14 (100)
Non-levodopa-responsive freezing of gait	0/19 (0)	2/19 (11)	3/19 (16)	7/19 (37) [*11/19 (58)]	9/14 (64)
Postural hypotension (requiring pharmacological treatment)	0/19 (0)	1/19 (5)	1/19 (5)	3/19 (16) [*6/19 (32)]	5/14 (36)
Constipation (requiring pharmacological treatment)	2/19 (11)	2/19 (11)	5/19 (26)	7/19 (37) [*10/19 (53)]	7/14 (50)
Urinary incontinence	0/19 (0)	0/19 (0)	4/19 (21)	7/19 (37) [*12/19 (63)]	8/14 (57)
Speech disturbances	3/19 (16)	5/19 (26)	7/19 (37)	10/19 (53) [*12/19 (63)]	9/14 (64)
Dysphagia	1/19 (5)	2/19 (11)	6/19 (32)	11/19 (58) [*14/19 (74)]	12/14 (86)
Severe dysphagia (requiring percutaneous gastronomy)	0/19 (0)	0/19 (0)	0/19 (0)	0/19 (0) [*3/19 (16)]	3/14 (21)
Dementia	0/19 (0)	1/19 (5)	5/19 (26)	9/19 (47) [*10/19 (53)]	6/14 (43)
Mood depression (requiring pharmacological treatment)	0/19 (0)	2/19 (11)	4/19 (21)	8/19 (42) [*10/19 (53)]	6/14 (43)
Hallucinations (requiring pharmacological treatment)	2/19 (11)	2/19 (11)	5/19 (26)	9/19 (47) [*11/19 (58)]	9/14 (64)
L-dopa DOSE (mg)	714.38 ± 277.36 (250–1200)	216.30 ± 193.40 (0–600)	296.25 ± 207.15 (0–600)	470.80 ± 265.4 (150–1200)	417.30 ± 220.20 (150–900)
LEDD (mg)	890.38 ± 299 (325–1350)	336.50 ± 189.30 (50–800)	381.63 ± 180.46 (50–612.5)	488.90 ± 265.50 (150–1200)	435.10 ± 223.20 (150–900)

Asterisk indicates the cumulative number of patients at last follow-up available and mean levodopa equivalent daily dose (LEDD) and L-dopa dose values. Falls were defined as a score ⩾2 on item 13 of UPDRS, postural instability as a score ⩾2 on item 30, non-levodopa-responsive freezing of gait as a score ⩾2 on item 14 in 'on–condition', urinary incontinence as the need to use a diaper or a catheter, dysphagia as a score ⩾2 on item 7 and speech difficulties as a score ⩾2 on item 18. Pharmacological treatments for postural hypotension, constipation, mood depression and hallucinations were prescribed, according to the clinical evaluation, in patients reporting moderate to severe clinical symptoms. Patients treated with antidepressant drugs showed a Beck Depression Inventory score ⩾18. STN = subthalamic nucleus.

Dementia, mood depression, hallucinations and neuropsychological assessment

Patients were accurately screened for dementia at baseline, considering that significant cognitive function impairment is an exclusion criterion for subthalamic nucleus DBS. However, 5% of patients ($P = 0.317$) met the diagnostic criteria for dementia (DSM-IV-TR; American Psychiatric Association, 2000) at the first year evaluation, 26% at the third year ($P = 0.015$) and >40% at the fifth and at the seventh year ($P < 0.001$). Neuropsychological data showed a progressive worsening in executive functions, reasoning, language and memory (Table 4), and the number of subjects requiring antipsychotic therapies significantly increased at 5 and >7 years ($P = 0.001$). In addition, the mean score of UPDRS -I significantly worsened from the baseline to the fifth year ($P = 0.049$) and to the last follow-up evaluation ($P = 0.001$). A significant increase was also observed in the prescription of antidepressant drugs, which increased from a baseline value of 0% to >40% at 5 years and at >7 years from surgery ($P = 0.001$). The time to event survival curves reported in Fig. 5 showed a steep decline in the percentages of patients without mood depression, hallucinations and dementia after the 25 years timeline of disease duration: the median duration of disease at the time of onset of these symptoms was 30.9 years (95% CI: 29.95–31.84 years) for hallucinations, 32 years for dementia (95% CI: 30.1–33.9 years) and 31.74 (95% CI: 29.5–33.9 years) for mood depression. The survival distributions of these symptoms were not significantly influenced by gender, Parkinson's disease clinical feature and age at the Parkinson's disease onset.

Discussion

This study describes the clinical evolution of a cohort of 19 patients with Parkinson's disease, treated with subthalamic nucleus DBS after more than 20 years of disease, and followed up to a mean of 30 years from the onset of Parkinson's disease. At the 20 year baseline of this study (range 20–28 years), a strict evaluation excluded the presence of dementia and relevant non-levodopa-responsive symptoms, confirming the eligibility for the neurosurgical treatment; the successive clinical and neuropsychological assessments investigated the rate of progression of motor and non-motor symptoms, in relation to both the years elapsed from the disease onset and the subthalamic nucleus DBS follow-up duration. The majority of patients progressively developed falls (64%), postural instability (100%), non-levodopa-responsive freezing of gait (64%), dysphagia (86%), urinary incontinence (57%), severe postural hypotension (36%) and dementia (43%) during the course of follow-up. On the other hand, neuropsychological data showed a gradual decline in the performance of all the main cognitive domains, in agreement with previous findings that showed a 5-fold prevalence of dementia in patients with Parkinson's disease compared to the general population (Hobson and Meara, 2004). The pattern of cognitive function involvement showed the typical features of Parkinson's disease-associated cognitive decline (Caballol et al., 2007), with an initial dysexecutive syndrome, frequently accompanied by hallucinations and depression, followed by a progressive impairment of language, reasoning and memory.

The young age at onset and the possible inclusion of some patients with a genetic parkinsonism might explain the mild disease evolution of this cohort of patients, who met the strict CAPSIT-Parkinson's disease criteria after >20 years of disease. Considering that a lower incidence of dementia and other severe non-levodopa-responsive symptoms can be observed in genetic parkinsonisms (Inzelberg and Polyniki, 2010), one can speculate that, if these patients had been excluded from the cohort, the survival curves reporting the development of non-levodopa-responsive symptoms would have been even steeper. Unfortunately, genetic testing was not available for most patients, and a separate analysis of outcome could not be performed.

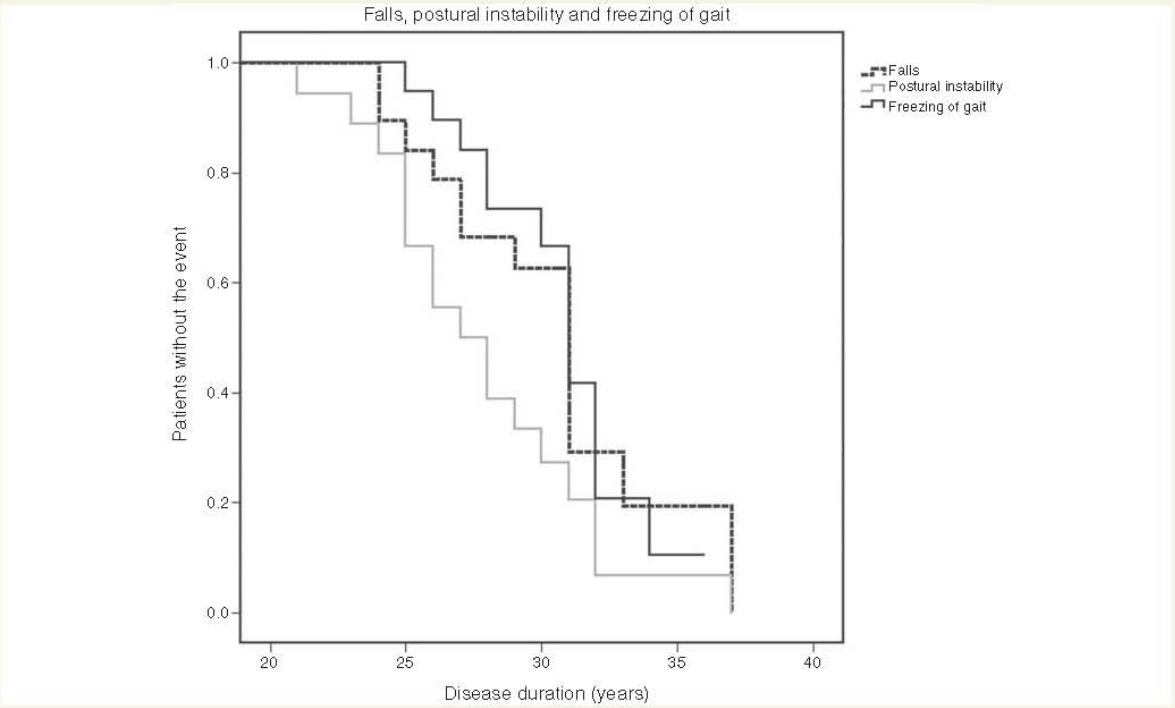

Figure 2 Survival curves for falls, postural instability and non-levodopa-responsive freezing of gait in relation to years of Parkinson's disease duration.

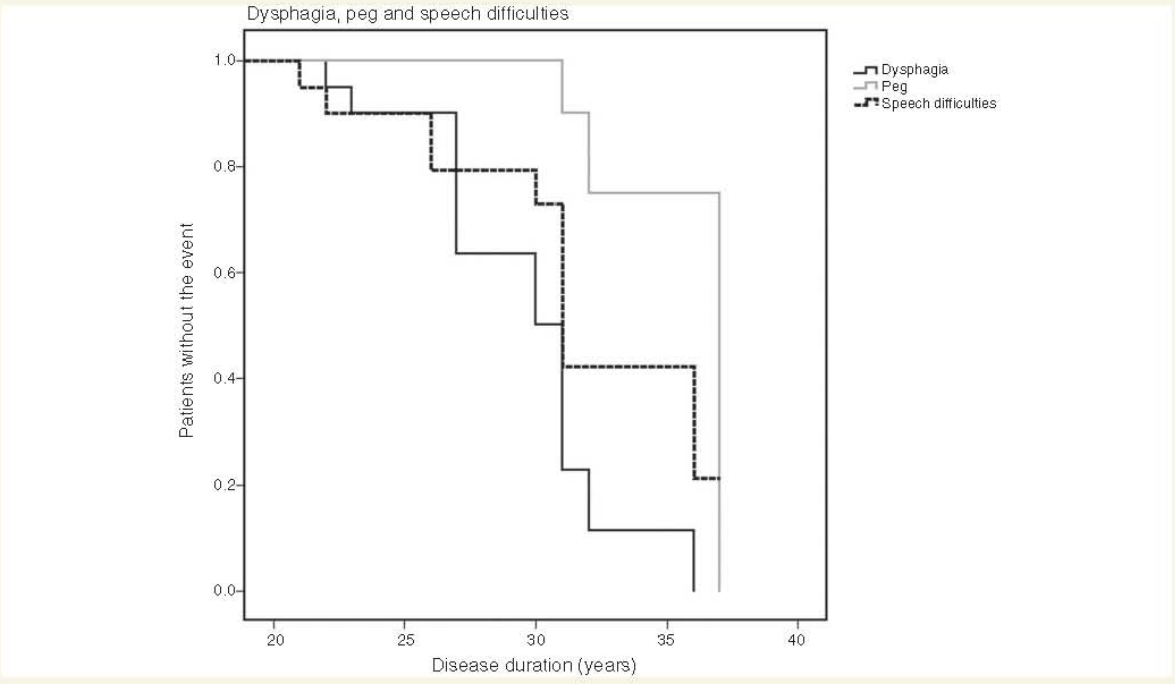

Figure 3 Survival curves for dysphagia, speech difficulties and patients requiring percutaneous gastrostomy in relation to years of Parkinson's disease duration.

Nevertheless, we found a global high rate of axial symptoms development during the course of follow-up, with a progressive lessening of both 'medication' and 'stimulation' effectiveness, and a global reduction in

the synergistic effect of the 'stimulation ON/medication ON' condition. The deterioration of axial symptoms, including speech, postural stability and non-levodopa-responsive freezing of gait have been previously described in subthalamic nucleus DBS-treated patients (Krack et al., 2003; Rodriguez-Oroz et al., 2005), as a combination of Parkinson's disease natural progression and dopaminergic therapies responsiveness parallel reduction.

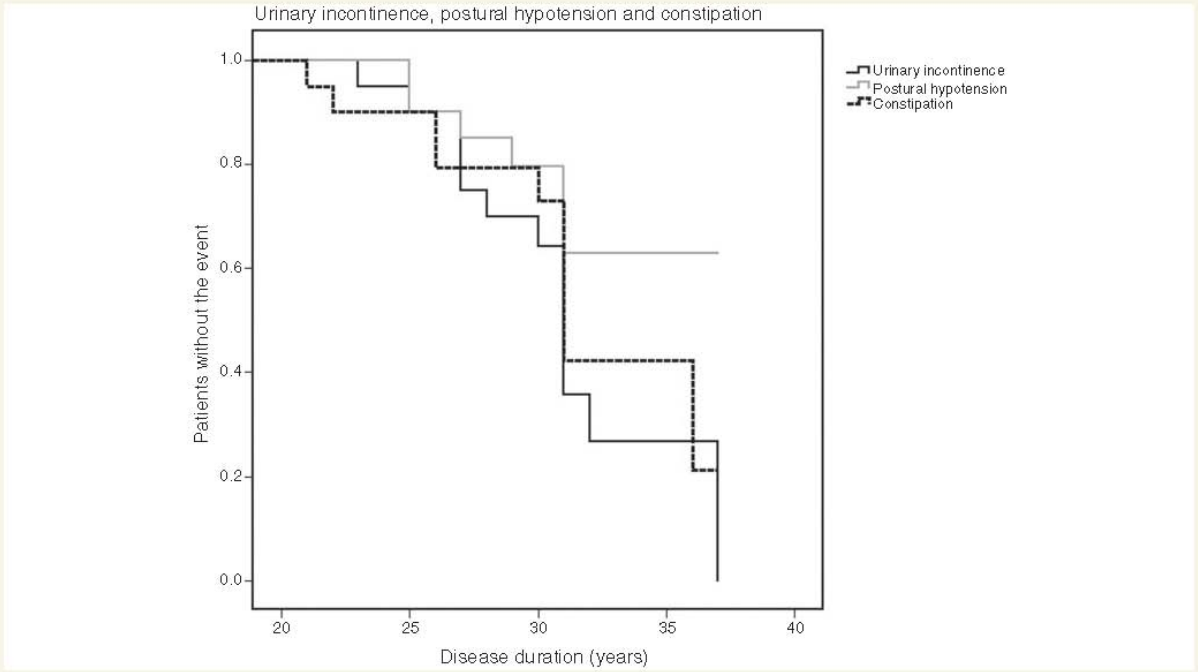

Figure 4 Survival curves for urinary incontinence and need of pharmacological treatments for constipation and postural hypotension in relation to years of Parkinson's disease duration.

Table 4 Percentages of patients reporting a significant impairment for each cognitive domain at different follow-up durations

Cognitive domains	Baseline (%)	1 year after STN DBS (%)	3 years after STN DBS (%)	5 years after STN DBS (%)	>7 years after STN DBS (%)
Reasoning	2/19 (11)	3/19 (16)	6/19 (31)	8/19 (42)	6/14 (42)
Memory	1/19 (5)	1/19 (5)	3/19 (16)	4/19 (21)	3/14 (21)
Executive functions	2/19 (11)	7/19 (37)	6/19 (32)	9/19 (47)	6/14 (42)
Language	0/19 (0)	1/19 (5)	5/19 (26)	8/19 (42)	5/14 (36)

STN = subthalamic nucleus.

The results of a recent meta-regression analysis (St George et al., 2010) showed that postural instability and gait disability progress over time in patients treated with subthalamic nucleus DBS. The initial positive effects of subthalamic nucleus DBS on balance and postural stability, which was reported by most authors in the first years from surgery, seem to be mostly related to the improvement of rigidity and bradykinesia, rather than on a specific effect on balance and gait. A milder impairment of gait and postural stability, however, was instead observed in patients treated with globus pallidus pars interna DBS, although this observation should be tempered by the fact that fewer long-term studies on globus pallidus pars interna DBS are available.

On the other hand, some degree of variability might be observed in the results of long-term subthalamic nucleus DBS clinical studies, likely reflecting a combination of factors, such as disease duration at the time of subthalamic nucleus DBS and age at Parkinson's disease onset.

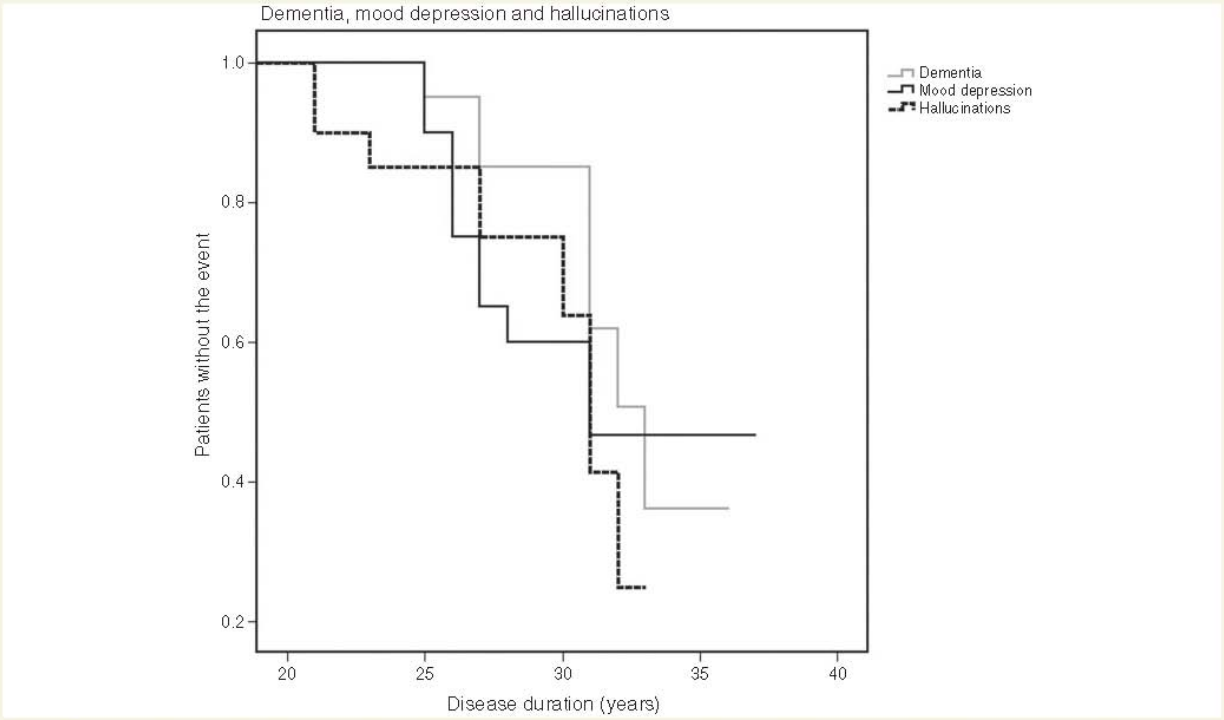

Figure 5 Survival curves for dementia and need of pharmacological treatments for mood depression and hallucinations in relation to years of Parkinson's disease duration.

In comparison with our data, Fasano and colleagues (2010) found a lower rate of dementia and postural instability at 5 and 8 years from surgery. However, the cohort of patients described by the authors had a significantly lower disease duration at subthalamic nucleus DBS (14 versus the 22.84 years of the present study) with a slightly older age at Parkinson's disease onset (43 versus 38.63 years). A progressive development of non-levodopa-responsive symptoms was instead observed over the 5- to 6-year evaluation period in several patients enrolled in a long-term DBS multicentre study (Moro et al., 2010), where the mean age at Parkinson's disease onset was 46 years old and the mean disease duration was 13.5 years. The role of age at surgery on the subthalamic nucleus DBS clinical outcome was addressed by several studies (Welter et al., 2002; Derost et al., 2007) that found a higher extent of improvement and a lower incidence of axial symptoms in younger patients with shorter disease duration, although a significant improvement of motor fluctuations and dyskinesias was also described in older patients (Russmann et al., 2004). Altogether these data are consistent with the hypothesis that age at surgery, disease duration and age at Parkinson's disease onset might play a significant role in the long-term subthalamic nucleus DBS clinical outcome, raising the question of whether the subthalamic nucleus DBS surgical option should be proposed earlier in the disease course.

In this study, we specifically addressed the issue of the role of disease duration on Parkinson's disease clinical course, describing the long-term evolution of a selected cohort of patients beyond 20 years of disease. Our main findings suggest that, in spite of the prior clinical evolution and the young age at onset, non-levodopa-responsive symptoms progressively emerged during the follow-up; in fact, at 30 years from the disease onset, >70% of subjects showed dementia, falls, dysphagia or urinary incontinence. In the Sydney Multicentre Study (Hely et al., 1999, 2005, 2008), a similar progression of Parkinson's disease non-

levodopa-responsive features was reported between 15 and 20 years of disease; at 15 years (Hely et al., 2005), falls were observed in 35% of patients, speech difficulties in 27%, dementia in 48% and urinary incontinence in 41%. An additional worsening was observed at 20 years (Hely et al., 2008), when >80% of patients developed falls, speech difficulties and dementia. The different temporal progression observed between our study and the Sydney Multicentre Study can be first explained by the selection criteria of the two cohorts of patients; in fact, we considered a selected group of patients with Parkinson's disease that met the strict CAPSIT-Parkinson's disease criteria after 20 years of disease, while the Sydney Multicentre cohort was representative of a more general Parkinson's disease population. In addition, the clinical outcome of the two groups was possibly influenced by numerous factors, such as the age at Parkinson's disease onset, which was 39 years of age in our cohort and 54 years of age in the Sydney Multicentre Study cohort (Hely et al., 2008). It has been shown that younger age at onset is generally associated with a slower disease progression (Schrag et al., 1998; Kempster et al., 2007) and with a higher prevalence of genetic parkinsonisms (Lucking et al., 2000; Klein et al., 2005). However, considering that a delay of ~10–15 years in the development of non-levodopa-responsive symptoms seems to be the main difference between our group of patients and the Sydney Multicentre Study cohort, it can be argued that similar clinical features were reached at a similar age by both groups. To support this argument, one can observe that postural instability, falls, speech difficulties, dysphagia, postural hypotension, severe constipation, urinary incontinence and dementia similarly occurred in the majority of patients at ~70 years of age. These findings are in agreement with the results of Kempster et al. (2007), who retrospectively reviewed the clinical data of 97 patients with Parkinson's disease, observing that younger age at onset was associated with a slower disease progression, although the main disability milestones were reached at a similar age by both the young-onset and the late-onset Parkinson's disease subgroups of patients. Moreover, in a recent paper (Kempster et al., 2010) the same authors analysed the clinical and neuropathological data of 129 patients with Parkinson's disease, observing that, even if younger age at onset was associated with a longer response to dopaminergic therapies, the appearance of specific symptoms, such as falls, visual hallucinations and cognitive disability, inevitably lead to a hastening of disease progression. These data are in agreement with the main results of this study, which is to our knowledge the first investigation reporting the clinical and neuropsychological data at 30 years from the Parkinson's disease onset. Unfortunately, it is not possible to determine whether the neurosurgical procedure of subthalamic nucleus DBS might have played a role in the disease progression. Even if ageing has been suggested as a prognostic factor for the neurosurgical outcome (Ory-Magne et al., 2007; Tsai et al., 2009; Parent et al., 2010), studies addressing the issue of long-term clinical evolution in early-onset versus late-onset subthalamic nucleus DBS subgroups of patients are still lacking.

Finally, this study has some limitations. First, the results refer only to a selected cohort of patients that probably represents a small portion of the general Parkinson's disease population; second, some patients with a genetic parkinsonism may possibly had been included in this cohort, thus affecting the long-term clinical and neuropsychological findings; third, the effects of subthalamic nucleus DBS on the disease progression cannot be completely excluded.

In conclusion, the main findings of our study suggest that even subgroups of patients with a milder disease course and early onset Parkinson's disease may eventually show decay in the effectiveness of subthalamic nucleus DBS and dopaminergic therapies, while the development of non-levodopa-responsive features seems to become the main cause of disability in a significant percentage of patients during the disease progression. One can, therefore, speculate whether the subthalamic nucleus DBS surgical option should be proposed earlier, considering that Parkinson's disease progression might not follow a linear course, and it is possible that age might influence the development of non-motor features more than disease duration.

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