Subthalamic nucleus deep brain stimulation outcome in young onset Parkinson's disease: a role for age at disease onset?

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Aristide Merola, Maurizio Zibetti, Carlo Alberto Artusi, Alice Marchisio, Valeria Ricchi, Laura Rizzi, Serena Angrisano, Nichy Arduino, Michele Lanotte, Mario Rizzone, Leonardo Lopiano

Department of Neuroscience, University of Turin, Turin, Italy
Correspondence to Dr. A. Merola, Department of Neuroscience, University of Turin, Via Cherasco 15, Torino 10126, Italy; aristidemerola@hotmail.com

Abstract

Background *Patients with young onset Parkinson's disease (YOPD) are often candidates for subthalamic nucleus–deep brain stimulation (STN–DBS). Nevertheless, few data have been reported on the long term STN–DBS clinical outcome of YOPD versus non-young onset Parkinson's disease (n-YOPD) patients.*
Aim *In this study, the issue of whether YOPD might represent a long term positive predictive factor for STN–DBS was addressed, comparing follow-up data for 20 YOPD and 40 n-YOPD patients (20 treated after <15 years of disease duration and 20 treated after ≥15 years of disease duration).*
Materials and methods *Mean scores for the Unified Parkinson's Disease Rating Scale (UPDRS) sections were compared 1 year, 5 years and, for 34 patients (12 YOPD and 22 n-YOPD), ≥7 years after surgery. Furthermore, a Cox proportional hazard regression model was used to determine the influence of age at PD onset, clinical phenotype, disease duration and duration of motor complications on the development of stimulation and medication resistant symptoms.*
Results *YOPD patients showed a lower incidence of stimulation and medication resistant symptoms and a lower mortality rate; also, the tremor dominant clinical phenotype was associated with a lower risk of developing dementia, hallucinations and constipation. No significant differences in UPDRS scores were observed between n-YOPD patients treated after <15 years of PD and those treated after ≥15 years of PD.*
Conclusion *In this series of STN–DBS treated patients, YOPD was associated with a medium to long term lower incidence of stimulation and medication resistant symptoms.*

Introduction

Young onset Parkinson's disease (YOPD) is usually characterised by a slower disease evolution and a more pronounced response to dopaminergic therapies,[1 2] with an even milder disease progression in the case of the tremor dominant (TD) clinical phenotype.[3 4] The term YOPD refers to patients with a PD onset between the ages of 21 and 40,[1] although subjects younger than 50 years might be considered as having early onset PD.[5] Schrag et al described the main clinical features of YOPD,[1] reporting a significantly lower risk of developing falls and freezing of gait but a higher risk of developing levodopa related motor fluctuations and dyskinesias during the course of the disease. Moreover, Jankovic and colleagues[4] found that YOPD took significantly longer (2.9 years) than late onset PD (1.7 years) to reach Hoehn and Yahr stage 1, thus supporting the hypothesis that different patterns of disease evolution can be observed in relation to the age of patients at the onset of disease.
Nevertheless, there are only few data on the role of age at PD onset on the outcome of patients treated with subthalamic nucleus–deep brain stimulation (STN–DBS).[6] In fact, the majority of studies have focused

on the predictive role of age at surgery,[7–11] reporting a higher progression rate of axial symptoms in older patients. This aspect might prove particularly relevant, considering that axial symptoms represent the main factor influencing the functional autonomy of STN–DBS treated patients.[12–17] However, considering the heterogeneity of PD clinical progression,[18] it can be argued that patients with a similar age can arrive at STN–DBS after a wide range of disease durations.

Otaka and colleagues[6] recently reported the results of a short term comparison between 15 YOPD and 113 non-YOPD (n-YOPD) patients 6 months after surgery; the authors observed greater improvement in the Unified Parkinson's Disease Rating Scale (UPDRS)[19] motor score in the YOPD group, although the n-YOPD group underwent STN–DBS after a significantly shorter disease duration (9.8 years vs 17.8 years).

The majority of long term STN–DBS studies report that the effectiveness of stimulation on resting tremor and rigidity does not decline with disease progression,[12–17] while a gradual worsening of axial symptoms progressively affects most patients, leading to the development of stimulation and medication resistant symptoms. However, considering that patients with very different ages at PD onset (from the third to the seventh decades of life) were included in these studies,[12–17] and taking into account the milder natural course of YOPD, one can speculate that a different long term clinical evolution could have been observed between the YOPD and n-YOPD patients.

In order to evaluate the predictive role of age at PD onset on STN–DBS outcome, we retrospectively studied a cohort of YOPD and n-YOPD patients with respect to the possible influence of clinical phenotype, disease duration and duration of motor complications on the development of stimulation and medication resistant symptoms. Follow-up data were compared 1, 5 and ≥7 years after surgery.

Considering that YOPD and n-YOPD patients may show significantly different disease durations at surgery, which can often be longer than 15 years for YOPD,[6] we considered three separate groups of patients: 20 YOPD patients with a variable age at surgery; 20 n-YOPD patients treated with STN–DBS after ≥15 years of disease duration; and 20 n-YOPD patients treated with STN–DBS after <15 years of disease duration.

Materials and methods

All 60 patients enrolled in this study had undergone STN–DBS at our centre between 1998 and 2005. Three subgroups were considered, each one consisting of 20 subjects, consecutively included according to the following selection criteria: age <40 years at PD onset independent of disease duration at surgery; age ≥40 years at PD onset with a disease duration ≥15 years at surgery; age ≥40 years at PD onset with a disease duration <15 years at surgery. When possible, subjects were evaluated every year, following the clinical and neuropsychological assessment recommended in the CAPSIT-PD protocol.[20] Mean follow-up duration at the first year was 1.17±0.25 in YOPD and 1.13±0.21 in n-YOPD patients and mean follow-up duration at the fifth year was 5.35±0.5 years in YOPD and 5.21±0.7 years in n-YOPD patients. In the subgroup of patients with a follow-up duration ≥7 years, we considered the last evaluation available, with a mean duration of 7.95±1.4 years in YOPD and 7.8± 1.2 years in n-YOPD patients.

Clinical data obtained at baseline were compared with those obtained 1 year, 5 years and, for 34 subjects (12 YOPD and 22 n-YOPD), ≥7 years after surgery. The STN–DBS surgical treatment was performed in accordance with the procedure previously described elsewhere[21] and all subjects included in this study gave informed consent to use the clinical data collected at each evaluation for scientific purposes.

Clinical assessment

A complete UPDRS evaluation was carried out at baseline (before STN–DBS), both in the 'off condition' (at

least 12 h after the last levodopa dose) and in 'on-condition' (40 min after administration of a levodopa challenge dose, consisting of 1.5 times the usual morning dose). Following the CAPSIT-PD protocol,[20] the same evaluation was performed at follow-up waiting at least 60 min after the stimulation was switched off and 30 min after the stimulation was switched on, under the following four conditions: (1) stimulation ON/medication OFF (Stim-ON/Med-OFF); (2) stimulation OFF/medication OFF (Stim-OFF/Med-OFF); (3) stimulation OFF/medication ON (Stim-OFF/Med-ON); and (4) stimulation ON/medication ON (Stim-ON/Med-ON). In addition, the UPDRS-III axial subscore was calculated as the sum of items 18 (speech), 22 (neck rigidity), 27 (arising from a chair), 28 (posture), 29 (gait) and 30 (postural stability). Patients were also classified as having the TD or akinetic rigid (AR) PD subtype, according to the criteria suggested by Jankovic and colleagues.[4]

Moreover, all subjects underwent a standardised battery of cognitive tests, assessing reasoning (Raven Colour Matrices), memory (Bi-syllabic 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). Mood depression was assessed by means of the Beck Depression Inventory and dementia was defined by impairment of two or more cognitive domains according to the diagnostic criteria of the American Psychiatric Association.[22] Clinical data on stimulation and medication resistant symptoms were collected by means of the UPDRS items and a clinical interview: patients were evaluated for falls (score ≥2 on item 13 of the UPDRS), dysphagia (score ≥2 on item 7), dysarthria (score ≥2 on item 18), hallucinations (score ≥2 on item 2), mood depression (Beck Depression Inventory score ≥18 and/or requiring pharmacological treatment) and dementia, as previously defined.[22] Moreover, additional information on bladder and bowel functions were also collected, evaluating the need to use a diaper or a catheter for urinary incontinence and the requirement for pharmacological treatments (macrogol, strong laxatives or enemas) for constipation.

Statistical analysis

The primary outcome of this study was comparison of the clinical evolution of YOPD and n-YOPD patients over a follow-up period of 5 years and, for a subgroup of patients, ≥7 years. Secondary outcomes included comparison of the two subgroups of n-YOPD patients (subjected to STN–DBS after <15 years or ≥15 years of disease duration) and estimation of the HR of developing stimulation and medication resistant symptoms in patients with different ages at onset (<40 vs ≥40 years), clinical phenotype (TD vs AR), disease duration and duration of motor fluctuations. The Mann–Whitney U test and the Kruskal–Wallis test were used for comparisons between different groups at baseline, while comparison at different timelines (baseline, 1 year, 5 years, ≥7 years) was performed by means of the Friedmann rank sum test and, when appropriate, the Wilcoxon rank sum test. Moreover, a repeated measures general linear model was applied for comparison of outcomes between groups. HR were calculated by means of a Cox proportional hazard regression model, considering all follow-up data available for each patient; YOPD and n-YOPD mortality rates were compared using the Kaplan–Meier survival analysis log rank test. Analyses were performed using PASWStat V.18 for Windows; all p values reported are two-tailed and 0.05 was considered the statistical threshold.

Results

Baseline differences between groups

As shown in table 1, although the three subgroups showed a similar baseline UPDRS for the main section scores, a significant difference in age at surgery was observed between the two n-YOPD subgroups of

patients (p=0.03) and between the YOPD and n-YOPD groups (p=0.01). Moreover, significantly different disease duration was observed in the n-YOPD group of patients treated with STN–DBS after <15 years of PD (p=0.002 compared with the YOPD group; p=0.005 compared with the n-YOPD group treated with STN–DBS after ≥15 years of PD). Finally, the YOPD group showed a lower age at PD onset compared with the n-YOPD group (p<0.001) while the two subgroups of n-YOPD patients did not differ significantly for age at PD onset (p=0.21).

Follow-up evaluation

All subjects in the YOPD group and 38 of 40 subjects in the n-YOPD group completed the 5 year follow-up period (5.35±0.5 years in YOPD patients; 5.21±0.7 years in n-YOPD patients). Two subjects in the n-YOPD group (one in the subgroup treated ≥15 years and one in the subgroup treated <15 years after disease onset) were lost to follow-up and consequently were excluded from the analyses. Additional data were available for 34 patients (12 YOPD and 22 n-YOPD) ≥7 years after surgery (7.95±1.4 years in YOPD patients; 7.8±1.2 years in n-YOPD patients).

Table 1 Main baseline clinical and demographic characteristics of the three groups of patients

		n-YOPD	
	YOPD	≥15 years at STN–DBS	<15 years at STN–DBS
No of subjects	20	20	20
Gender (M:F)	11:9	13:7	11:9
Clinical phenotype (TD:AR)	13:7	13:7	10:10
Age at disease onset (years)	35.5±4.7† (24–39)	46.8±3.7 (41–53)	48.5±4.1 (40–59)
Disease duration at STN–DBS	19.2±5.3 (10–28)	18.4±2.6‡ (15–24)	12.5±1.3‡ (10–14)
Age at surgery (years)	54.7±4.8* (46–63)	65.5±3.0* (58–69)	60.6±4.5* (50–68)
UPDRS-I	1.65±1.94	1.84±1.56	1.57±1.60
UPDRS-II 'Med-ON'	8.67±5.91	8.5±6.30	7.14±4.03
UPDRS-II 'Med-OFF'	24.4±7.25	26.06±7.27	23.52±6.02
UPDRS-III 'Med-ON'	17.7±8.82	20.3±9.76	15.973±5.7
UPDRS-III 'Med-OFF'	54.8±17.4	55.56±12.76	51.25±8.71
Axial subscore 'Med-ON'	8.50±4.57	9.48±4.73	8.37±3.63
UPDRS-IV	10.2±2.76	9.38±3.48	8.64±2.60
UPDRS V 'Med-OFF'	3.92±1	3.92±0.79	3.55±0.845
Schwab and England SCALE 'Med-ON'	85.5±13	84±17.01	89.11±9.39

Values are mean±SD (range) or number.
*p<0.05 comparing all subgroups with each other.
†p<0.05 YOPD compared with n-YOPD patients.
‡p<0.05 comparing the two subgroups of n-YOPD patients.
AR, akinetic rigid clinical; 'Med-ON', evaluation performed under the pharmacological effect of dopaminergic therapies; 'Med-OFF', evaluation performed at least 12 h after the last levodopa dose; n-YOPD, non-young onset Parkinson's disease; STN–DBS, subthalamic nucleus–deep brain stimulation; TD, tremor dominant; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young onset Parkinson's disease.

Table 2 UPDRS section mean scores in YOPD and n-YOPD patients at different follow-up times (baseline, 1 year and 5 years)

	Group	Baseline (20 YOPD, 40 n-YOPD)	1 year (20 YOPD, 40 n-YOPD)	5 years (20 YOPD, 38 n-YOPD)
UPDRS-I	YOPD	1.65±1.94	1.68±1.67	2.63±2.49
	n-YOPD	1.72±1.58	1.71±1.98	4.01±2.70*
UPDRS-II 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	8.67±5.91	9.73±5.43	10.55±9.83
	n-YOPD	7.44±5.52	9.11±5.19	17.22±9.46*
UPDRS-III 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	16.65±8.82	13.81±8.55	18.21±7.69
	n-YOPD	16.48±8.50	14.51±7.28	25.55±14.93*
UPDRS-III 'Stim-ON/Med-OFF' (Med-OFF at baseline)	YOPD	54.80±17.41	24.95±10.14	29.11±12.15
	n-YOPD	53.75±11.33	25.87±11.01	31.36±11.78*
UPDRS-III 'Stim-OFF/Med-OFF' (Med-OFF at baseline)	YOPD	54.80±17.41	58.05±16.16	60.01±16.12
	n-YOPD	53.75±11.33	57.90±14.33	58.12±13.71
Axial subscore 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	8.50±4.57	7.11±3.58	9.10±5.47
	n-YOPD	8.72±4.11	7.53±2.2	12.63±7.22*
UPDRS-IV	YOPD	10.22±2.77	2.23±2.61	3.82±2.86
	n-YOPD	9.08±3.14	2.19±3.12	3.80±2.75
Schwab and England Scale 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	85.50±11.08	86.31±10.65	83.08±11.66
	n-YOPD	86.07±11.50	86.51±12.59	78.47±15.48*

*$p<0.05$.
'Med-ON', evaluation performed under the pharmacological effect of dopaminergic therapies; 'Med-OFF', evaluation performed at least 12 h after the last levodopa dose; n-YOPD, non-young onset Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young onset Parkinson's disease.

Motor symptoms

A gradual lessening of stimulation and medication effectiveness was observed in patients in both the YOPD and n-YOPD groups. Comparing the follow-up values obtained the first year after surgery with those obtained after 5 years (table 2), and for a smaller group of patients after ≥7 years (table 3), significant worsening was observed in most cases. However, as shown in figure 1, the 'Stim-ON/Med-ON' UPDRS-III mean score declined significantly only ≥7 years after surgery in YOPD patients (p=0.025) while an earlier worsening was observed in n-YOPD patients from the fifth year of follow-up (p=0.017). Comparing baseline 'Med-OFF' values with the first year 'Stim-ON/Med-OFF' values, both groups showed a significant improvement in the UPDRS-III motor score (54% in YOPD, 52% in n-YOPD). However, the extent of stimulation effectiveness gradually decreased during follow-up; comparing the conditions 'Stim-ON/Med-OFF' and 'Stim-OFF/Med-OFF' after 1, 5 and ≥7 years of follow-up, the percentage efficacy of stimulation ranged from the 1 year value of 57% in YOPD and 55% in n-YOPD, to the 5 year value of 51% in YOPD and 44% in n-YOPD and to the ≥7 year value of 47% in YOPD and 34% in n-YOPD.
In addition, a worse axial subscore progression was observed in n-YOPD patients (p=0.022); in fact, significant worsening of the mean axial subscore occurred in the n-YOPD patients from the fifth year of follow-up (p=0.001) while significant worsening was observed after ≥7 years in the YOPD group (p=0.011). According to the Cox proportional hazard regression model, the n-YOPD group showed a higher risk of developing falls (HR=3.240; IC=1.336–7.859; p=0.009). Figure 2 shows the survival curves for falls in the two groups of patients; a steeper decline was observed in n-YOPD patients from the first years after surgery although the differences between the two curves progressively become wider around the fifth to eighth years of follow-up. An additional comparison between the two n-YOPD subgroups of patients (<15 or ≥15 years of disease duration at surgery) showed similar progression of UPDRS-III motor symptoms (p=0.104) and axial subscore (p=0.094). In both cases, a significant decline in UPDRS-III motor score was observed 5 years after surgery.

Table 3 UPDRS section mean score comparisons between baseline, 1 year and ≥7 years of follow-up in a subgroup of YOPD and n-YOPD patients

	Group	Baseline (12 YOPD, 22 n-YOPD)	1 year (12 YOPD, 22 n-YOPD)	≥7 years (12 YOPD, 22 n-YOPD)
UPDRS-I	YOPD	1.62±1.73	1.45±1.80	4.56±3.45*
	n-YOPD	1.66±1.83	1.34±1.62	6.17±2.09*
UPDRS-II 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	9.36±7.62	9.31±4.58	15.77±11.28*
	n-YOPD	8.95±6.41	9.06±5.46	19.02±8.22*
UPDRS-III 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	14.78±10.19	13.1±4.36	22.33±15.67*
	n-YOPD	17.66±9.86	15.54±7.1	32.14±15.48*
UPDRS-III 'Stim-ON/Med-OFF' (Med-OFF at baseline)	YOPD	53.36±20.13	23.25±12.11	31.93±19.13*
	n-YOPD	54.91±12.22	24.65±10.35	40.58±11.72*
UPDRS-III 'Stim-OFF/Med-OFF' (Med-OFF at baseline)	YOPD	53.36±20.13	55.86±21.64	61.17±17.20
	n-YOPD	54.91±12.22	56.78±13.02	61.02±12.56
Axial subscore 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	5.91±2.54	5.78±2.22	10.85±6.11*
	n-YOPD	6.12±2.75	5.91±2.86	15.03±6.41*
UPDRS-IV	YOPD	11.27±2.58	2.05±2.74	4.86±2.97*
	n-YOPD	8.95±3.17	2.33±4.21	4.52±2.68*
Schwab and England Scale 'Stim-ON/Med-ON' (Med-ON at baseline)	YOPD	86.03±13.56	89.02±6.99	78.18±17.22*
	n-YOPD	86.05±12.75	86.86±11.05	66.50±20.02*

*$p<0.05$.
'Med-ON', evaluation performed under the pharmacological effect of dopaminergic therapies; 'Med-OFF', evaluation performed at least 12 h after the last levodopa dose; n-YOPD, non-young onset Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young onset Parkinson's disease.

Stimulation and medication resistant symptoms

Several patients in both the YOPD and n-YOPD groups developed stimulation and medication resistant symptoms during the course of clinical observation. However, the n-YOPD group showed a significantly higher risk of developing dementia (HR=2.7; IC=1.03–7.21; p=0.043), hallucinations (HR=3.25; IC=1.12–9.45; p=0.03), dysarthria (HR=2.605; IC=1.169–5.807; p=0.019) and dysphagia (HR=2.66; IC=1.2–5.892; p=0.016). Moreover, the AR clinical phenotype was associated with a significantly higher risk of developing hallucinations (HR=2.14; IC=1.05–3.85; p=0.031), dementia (HR=2.11; IC=1.025–3.62; p=0.047) and need to use a pharmacological treatment for constipation (HR=6.628; IC=1.648–25.173, p=0.011) while disease duration at surgery or duration of motor complications were not significantly associated with the risk of developing stimulation and medication resistant symptoms.

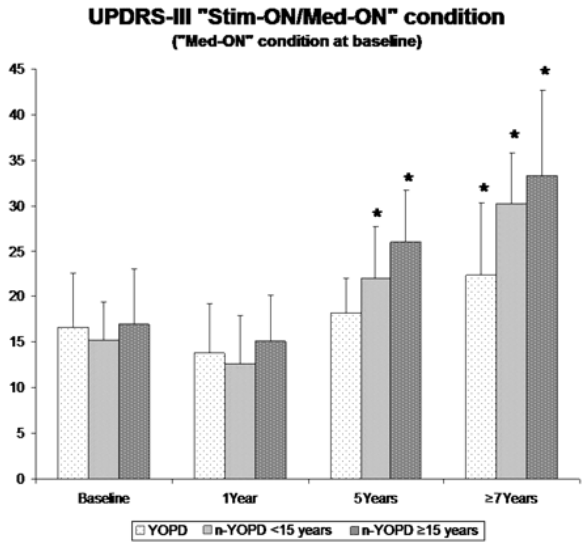

Figure 1: Mean score for the Unified Parkinson's Disease Rating Scale (UPDRS)-III under the 'Med-ON' condition (baseline) and the 'Stim-ON/Med-ON' condition (follow-up) in young onset Parkinson's disease (YOPD) patients and in the two subgroups of non-young onset Parkinson's disease (n-YOPD) patients. Compared with the first year after surgery, significant worsening (*) was observed in YOPD after ≥7 years while both n-YOPD subgroups of patients showed similar worsening from the fifth year.

Activities of daily living

According to the UPDRS-II mean score (tables 2 and 3), activities of daily living (ADL) significantly worsened in the group of n-YOPD patients from the fifth year of follow-up (p=0.003), with an even more pronounced decline after ≥7 years (p<0.001). On the other hand, the UPDRS-II mean score progression (figure 3) was milder in YOPD patients (p=0.03), showing significant worsening of ADL only in the subgroup of patients followed for ≥7 years after surgery (p=0.036).

The Schwab and England Scale, which provides global information on the patient's autonomy in the daily living activities, showed significant worsening in n-YOPD patients after 5 years of follow-up (p=0.031) while in the YOPD group a significant decline was observed only in the subgroup of patients followed for ≥7 years (p=0.016). Comparing the clinical outcome of the two n-YOPD subgroups of patients, no significant differences were observed in UPDRS-II (p=0.361) or in the Schwab and England Scale mean score progression (p=0.267).

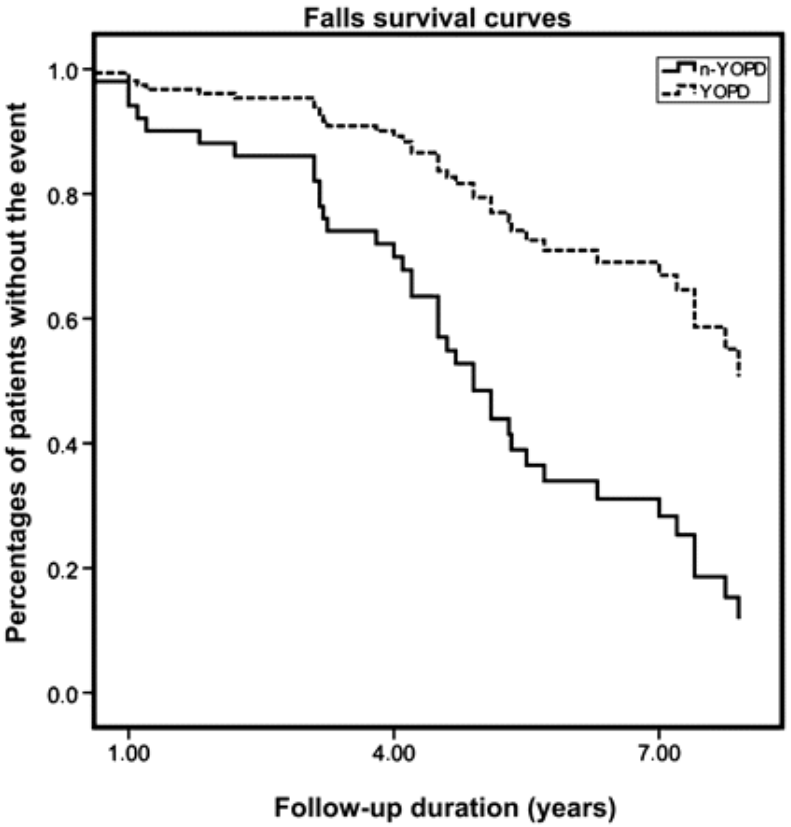

Figure 2: Survival curves for the development of falls in young onset Parkinson's disease (YOPD) and non-young onset Parkinson's disease (n-YOPD) patients.

Complications of therapy

According to the UPDRS-IV mean score (tables 2 and 3), complications of therapy significantly improved in both the YOPD (79.3%) and n-YOPD (67.6%) groups of patients in the first year after surgery. However, the overall improvement initially achieved partially decreased during the course of follow-up, with significant worsening in both groups after ≥7 years (table 3). No relevant differences were observed in the progression of UPDRS-IV mean score between the two subgroups of n-YOPD patients (p=0.236).

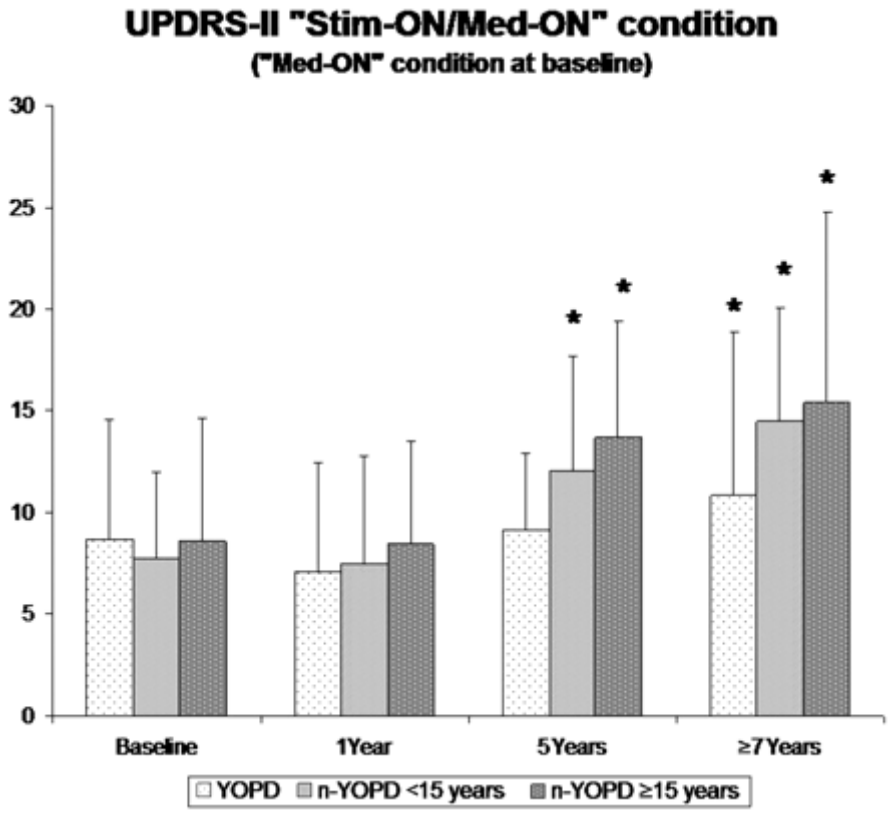

Figure 3: Mean score for the Unified Parkinson's Disease Rating Scale (UPDRS)-II under the 'Med-ON' condition (baseline) and the 'Stim-ON/Med-ON' condition (follow-up) in young onset Parkinson's disease (YOPD) patients and in the two subgroups of non-young onset Parkinson's disease (n-YOPD) patients. Both n-YOPD subgroups of patients showed similar worsening (*) 5 years after surgery, while a milder progression was observed in YOPD patients, with significant worsening only after the seventh year.

Neuropsychological outcome

Although differences in samples size and age at surgery between the two groups should be considered, significant differences were observed in neuropsychological outcomes between the two groups: dementia was observed in almost half (47.4%) of n-YOPD and in 25% of YOPD patients, after a median follow-up duration of 9.12 years in the YOPD (95% CI 6.3 to 9.8 years) and 6.43 years in the n-YOPD (95% CI 5.2 to 8.5 years) groups. Hallucinations occurred in 57.5% of n-YOPD patients and in 35% of YOPD patients, while mood depression affected both groups equally (60.5% in n-YOPD and 60% in YOPD patients). UPDRS-I mean score showed a steeper progression in the n-YOPD group (tables 2 and 3), with significant worsening from the fifth year of follow-up (p= 0.033), while in the YOPD group, only the subgroup of patients followed for

≥7 years (table 3) showed significant worsening of UPDRS-I (p=0.023). An equal proportion of patients affected by dementia (47.4%) were observed in the two subgroups of n-YOPD patients.

Levodopa equivalent daily dose (LEDD)

n-YOPD patients had significantly higher (p=0.008) levodopa equivalent daily dose (LEDD) values at baseline (1160.77±462.65 mg vs 865.55±348.59 mg). However, both groups showed a similar reduction in mean LEDD values between baseline and the first year after surgery (−55% in n-YOPD and −59% in YOPD patients). A similar slight increase in mean LEDD values, which did not reach statistical significance, was observed in the following years.

Mortality rate

Differences in samples size and age at surgery between the two groups should be considered for mortality rates; with these limits, lower mortality was observed in YOPD patients (5% vs 21% of n-YOPD patients; p=0.031).

Discussion

The main aim of this study was to determine whether YOPD and n-YOPD patients show a different long term outcome after STN–DBS. Clinical studies suggest that YOPD patients are usually characterised by a slower disease progression, lower incidence of non-levodopa responsive symptoms and more severe motor complications,[1–4] thus representing ideal candidates for the DBS surgical option. However, at the present time, there are only few data on the predictive role of age at PD onset on STN–DBS clinical outcome[7 23]; to our knowledge, no study has specifically addressed the issue of whether a different long term outcome is observed in YOPD and n-YOPD patients after STN–DBS.

In this study, we retrospectively compared the clinical progression of 20 YOPD and 40 n-YOPD patients treated with STN–DBS, evaluating the role of age at PD onset on clinical outcome at 5 years and, for a subgroup of patients, after ≥7 years of follow-up.

Although there were several baseline clinical differences between the groups, YOPD patients showed a milder worsening of ADL and the UPDRS axial subscore. Moreover, in these limited series of subjects, we observed a lower mortality rate and a lower risk of developing falls, dementia, hallucinations and dysphagia in YOPD patients. A lower risk of developing dementia, hallucinations and constipation was also observed in patients with the TD clinical phenotype.

Our results are in agreement with previous studies[13–18] which suggest that a partial decrease in STN–DBS effectiveness progressively occurs in advanced PD patients, as a consequence of the gradual development of medication and stimulation resistant symptoms. Interestingly, LEDD values did not significantly increase during follow-up in either YOPD or n-YOPD patients. This may indirectly suggest that the development of stimulation and medication resistant symptoms or levodopa related side effects, such as dyskinesias, might have partially limited the possibility of increasing the dose of dopaminergic therapies.

Nevertheless, we observed that a separate assessment of YOPD and n-YOPD patients can provide further information on the predictive factors associated with the STN–DBS long term clinical outcome. In fact, according to Piboolnurak and colleagues,[24] the preoperative response to levodopa did not completely predict the long term STN–DBS outcome. Moreover, Fasano and colleagues[13] observed that the baseline functional impairment of gait and postural stability might be associated with decreased long term STN–DBS

effectiveness. In the present study, we found a milder clinical evolution in YOPD patients, in spite of a longer disease duration, and an axial impairment similar to the n-YOPD group at the time of surgery.

A recent meta-regression analysis of the long term effects of DBS in PD25 indicates that DBS of the globus pallidus pars interna (GPi) might preserve balance and gait better than STN–DBS. Nevertheless, patients treated with GPi–DBS had a lower age at PD onset; therefore, it can be argued that the better clinical outcome observed with GPi–DBS on balance and gait might have also been influenced by age at PD onset.

In addition, the possible influence of genetic factors should also be considered; younger age at PD onset has been associated with a higher prevalence of genetic parkinsonisms[26–29] that might present with a lower incidence of dementia and non-levodopa responsive symptoms.[30] Unfortunately, we could not obtain genetic data from the majority of patients included in this study and a separate assessment of outcomes could not be performed. A limited series of patients treated with STN–DBS, with different genetic mutations, have been reported in the literature[31–33] while a larger analysis was performed by Moro and colleagues[34] who did not find significant differences in a long term STN–DBS comparison between 12 patients with monogenic parkinsonisms and 68 sporadic PD patients with a similar age at disease onset (≤45 years).

Moreover, we compared two subgroups of n-YOPD patients with similar clinical symptoms at the time of surgery but treated with STN–DBS after <15 years (12.5±1.3) or ≥15 years (18.4±2.6 years) of PD. Although the second group showed a significantly longer disease duration, no relevant differences were observed in the clinical progression of these two series of n-YOPD patients, except for slightly worse axial symptom progression in the group treated after a longer disease duration. This may suggest that the development of stimulation and medication resistant symptoms does not seem to be influenced, in our series of patients, by disease duration per se.

In conclusion, the main findings of this retrospective study can be summarised as follows: (1) in this series of patients, n-YOPD patients showed significant worsening on the main UPDRS subscales after 5 year of follow-up, while significant worsening was observed in YOPD only after ≥7 years of follow-up; (2) worse progression of axial symptoms was observed in n-YOPD patients; (3) YOPD and TD clinical phenotype were associated with a lower risk of developing several medication and stimulation resistant symptoms; (4) no significant differences in UPDRS scores were observed after a follow-up period of 5 and ≥7 years between the two subgroups of n-YOPD patients (treated after <15 years or ≥15 years of PD).

Nevertheless, several important limits should be considered when interpreting the results of this study, including the younger age at surgery of the YOPD group, absence of genetic data and the clinical variability of a relatively small cohort of patients. Hence in order to better define the role of age at disease onset as a predictive factor of STN–DBS long term satisfactory outcome, our findings need to be confirmed in larger studies.

Competing interests: None.

Patient consent: Obtained.

Ethics approval: All subjects who took part in the study gave informed consent to be anonymously included in this publication. However, ethics committee approval was not requested because no experimental evaluations were performed; this study simply reports retrospective clinical data collected during ordinary clinical evaluations, which were performed in accordance with the principles of good clinical practice.

Provenance and peer review: Not commissioned; externally peer reviewed.

Contributors: AM was involved in the organisation and execution of the research project; design, execution, review and critique of the statistical analysis; writing of the first draft, and review and critique of the manuscript. MZ was involved in the organisation and execution of the research project; review and critique of the statistical analysis; and review and critique of the manuscript. CAA and AM were involved in the execution of the research project and in the analysis of the data. VR, NA and SA were involved in the execution of the research project, and review and critique of the statistical analysis. LR was involved in the analysis of the neuropsychological data. ML and MR were involved in the review and critique of the manuscript. LL was involved in the conception and organisation of the research project, critique of the statistical analysis, and review and critique of the manuscript.

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