Deep brain stimulation of the subthalamic nucleus in advanced Parkinson's disease: five year follow-up at a Portuguese center

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Introduction. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD) is safe and effective. Most series report stable long-term motor responses.

Aim. To report the long-term outcome of STN-DBS in advanced stage PD patients at a Portuguese center.

Patients and methods. Motor status was evaluated before surgery ('off' medication and best 'on'), post-operatively, and at five years ('on' medication and stimulation) using UPDRS part III. Axial symptoms subscores were quantified. Disability was assessed with the modified Rankin Scale (mRS). Development of dementia was assessed at 6 months and five years post-DBS.

Results. Of the 183 patients submitted to STN-DBS, 71 had completed 5 years of follow-up. Ten patients were not included: two died (cancer, myocardial infarction), five were lost to follow-up and three had their stimulation systems removed. Motor function improved by 78% and 66% postoperatively and at five years, respectively. There was improvement of axial symptoms postoperatively, with significant worsening at five years ($p < 0.001$). mRS scores improved postoperatively, but declined at five years, although most patients (88.5%) remained ambulatory (mRS < 4). One patient (1.6%) and 19 patients (31,2%) were demented at 6 months and 5 years, respectively. Patients who developed dementia were significantly older than non-demented patients (56.5 ± 7.8 vs 63.7 ± 5.9 years-old; $p < 0.001$).

Conclusions. In this series STN-DBS proved its efficacy regarding motor symptom improvement even five years after the procedure. Deterioration of axial symptoms and disability, as well as new onset dementia were observed in this period, but the possible role of STN-DBS as a causative factor is yet to be defined.

Key words. DBS. Deep brain stimulation. Dementia. Disability. Long term follow-up. Motor evaluation. Parkinson's disease. Subthalamic nucleus.

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder, and an often disabling one [1,2]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has proven to be effective and generally safe, with well characterized potential complications [3-9]. DBS may be more effective for the control of motor symptoms than best medical therapy, either alone or in combination with it [3,10,11]. Significant improvements in motor function and quality of life have been reported with STN-DBS in PD [11-13]. Reports on long-term outcomes of DBS for PD are limited, but studies describe generally stable motor responses with STN stimulation [4,7, 13-15]. Recent literature, however, highlights the potential cognitive effects, as a number of studies have reported cognitive decline after DBS, especially when STN is the target [10,16]. The prevalence of dementia in PD patients has been estimated at 30-40% [2], being this condition the most frequent exclusion criterion for DBS [8]. Assessment of long term efficacy and major complications of continued stimulation is extremely important. This matter gained additional relevance, as recently published evidence supports the use of STN-DBS at earlier stages of the disease [17]. Hence, the purpose of this study was to report the long-term outcome of STN-DBS for advanced PD patients at the first Portuguese center performing DBS.

Patients and methods

Sample

PD patients treated with STN-DBS at the Movement Disorders and Functional Surgery Unit of Centro

Hospitalar São João (Porto, Portugal) were included. Seventy-one consecutive patients underwent bilateral STN implants in the period between 2002 and 2007 and received continuous stimulation for 5 years.

Selection criteria of the Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease [9] were met by all subjects:

- Advanced clinically diagnosed PD following the United Kingdom Parkinson's Disease Society Brain Bank Criteria [18]; the diagnosis had been established for ≥ 5 years in all subjects.
- > 50% improvement in motor symptoms during an acute levodopa challenge.
- Untreatable motor fluctuations and dyskinesia, despite optimal adjustment of antiparkinsonian medication.
- No clinical signs suggesting an atypical parkinsonian disorder.
- Age ≤ 70 years.
- Absence of dementia or major ongoing psychiatric disorders (DSM-IV) [19].
- Absence of neurosurgical and neuroradiological contraindications.

Neurosurgical procedure

Stereotactic planning was carried out with preoperative 1.5 T MRI fused with stereotactic CT scan obtained on the day of surgery. A conventional procedure was followed to localize the anatomically defined target referenced to anterior commissure (AC)-posterior commissure (PC) (12 mm lateral, 2 mm posterior and 4 mm below the AC-PC line midpoint), followed by refinement of the final position through visual MRI inspection and manual adjustment, using the FrameLink Stealthstation ® (Medtronic, USA).

After intracranial surgical access, three to five leads were advanced for microrecording (typically three), followed by intraoperative test stimulation performed by the neurologist with the patient awake, to verify motor benefits and adverse effects. Patients were free from levodopa for 12 hours and at least one week without dopaminergic agonists, monoamino-oxidase inhibitors or amantadine, in order to detect significant motor changes under intraoperative stimulation.

The implantable pulse generator (IPG) was placed at the same surgical time, as previously described [20]. The IPG used was Kinetra ® (model 7428, Medtronic, USA). Post-operatively, continuous monopolar stimulation was used whenever possible, and bipolar stimulation was used in the event of limiting adverse effects. Stimulation parameters were 1.5-3.5 V, and pulse width 60-90 μs; most patients were kept on stimulation frequency of 130 Hz. Dopaminergic medication was reintroduced after surgery and kept at the minimum effective dose.

Motor evaluation

Patients were evaluated preoperatively (at baseline), assessed again at 1 and 6 months after surgery, and then every 6 months. Data was gathered from baseline presurgical assessment, at the first postoperative assessment (1 month), and 5 years after the procedure.

Two states were evaluated at baseline: off medication (≥ 12 h after the last levodopa dose) and on medication (benefit after administration of a dose of liquid levodopa that was 150% of the usual morning levodopa equivalent dose). At 1 month and 5 years postoperatively, patients were evaluated with the stimulators switched on and on medication (stimON/medON). The severity of motor symptoms was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) part III [21]. Axial symptoms were studied separately and were defined as the sum of the following motor subscores of UPDRS part III: speech, rising from a chair, posture, postural stability and gait (items 18, 27-30).

Medication was converted to levodopa equivalent daily dose (LEDD) for analysis [22] The treatment regimen was recorded preoperatively and compared to the medication requirements 1 month and 5 years after DBS.

Disability

This was measured using the modified Rankin Scale (mRS) [23], with scores ranging from 0 to 6. The mRS before surgery with patients on medication was compared to the score after 1 month and 5 years of surgery in the stimON/medON state.

Cognitive assessment

All patients underwent comprehensive neuropsychological evaluation prior to surgery, at 6 and 5 years postoperatively. Neuropsychological test batteries were administered by an experienced neuropsychologist. Measures included the Mini Mental State Examination, Frontal Assessment Battery, Clock Drawing Test, verbal fluency (semantic and phonemic), digit span, associative verbal memory and visual memory from the Wechsler Memory Scale, Stroop Test, Trail Making Test and Wisconsin Card Sorting Test.

All cognitive assessments before and after surgery were performed with the patients in pragmatically defined 'on'. Postoperative assessments were performed with the stimulators turned on. The presence of dementia was defined by the impairment in two or more cognitive domains and decline in the ability to perform activities of daily living (DSM-IV), not attributed to the motor impairment.

Statistical analysis

The primary outcome measures were the scores on UPDRS-III (total and axial subscores) at baseline, postoperatively (1 month after surgery) and at 5 years. Secondary outcomes were the degree of disability measured by the mRS, the medication requirements and the development of dementia at 5 years of bilateral STN stimulation.

Descriptive statistics were used for continuous variables, while categorical variables were described as percentage of subjects in each group. After assessing for normality of the distribution of samples, continuous data comparing baseline and postoperative motor scores and levodopa dosage were analyzed by means of the ANOVA repeated measures with Bonferroni post-hoc comparisons. Data comparing the modified Rankin Scale were analyzed using Friedman and Wilcoxon tests. For comparing the ages and disease progression between patients with and without dementia at 5 years, the independent t-test was used. All p values reported are two-tailed and a $p < 0.05$ was considered statistically significant.

Results

Descriptive analysis

A total of 183 patients underwent bilateral STN-DBS at our center. For 71 patients, 5 years had elapsed after the surgery, but only 61 where included: 5 patients did not attend the scheduled evaluations and were lost to follow-up, 2 patients died from unrelated causes (lung cancer and myocardial infarction) and 3 had their systems removed because of infection before completion of the follow-up period (Fig. 1). Two patients were excluded from motor evaluation due to impossibility to assess complete UPDRS-III scores (one had severe osteoarthrosis of the hip and knee joints preventing walking, and the other had a failed suicide attempt culminating in bilateral lower limb amputation), thus totalizing 59 patients for the motor evaluation.

Figure 1. Patient selection flowchart.

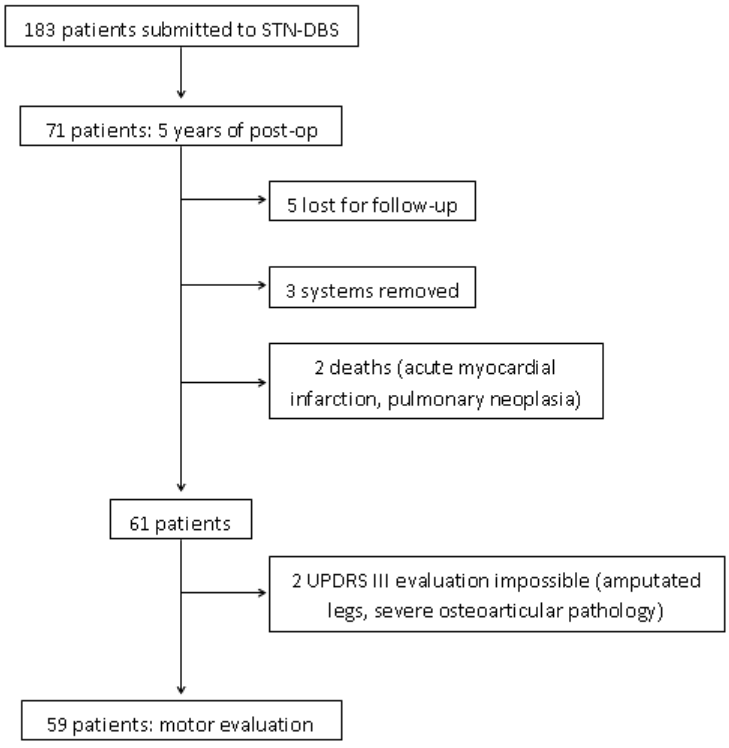

Table I. Baseline patient characteristics ($n = 59$).

Gender	Male	37 (63%)
	Female	22 (37%)
Age at onset of motor symptoms	≤ 40 years	17 (28.8%)
	> 40 years	42 (71.2%)
Age at surgery		58.6 ± 8.1 years (range: 33-70 years)
Disease duration at the time of surgery		14.0 ± 6.7 years

The main demographic characteristics of the studied population are summarized in table I.

Motor evaluation

At baseline, the total UPDRS-III score in the off medication state was 48.5 ± 11.2 and in the on medication state (medON) was 15.0 ± 5.7 (Fig. 2).

Figure 2. Motor evaluation. a) UPDRS III total score; b) Axial subscore; c) Levodopa equivalent daily dosage. [a] $p < 0.05$; [b] $p < 0.001$; ns: not significant.

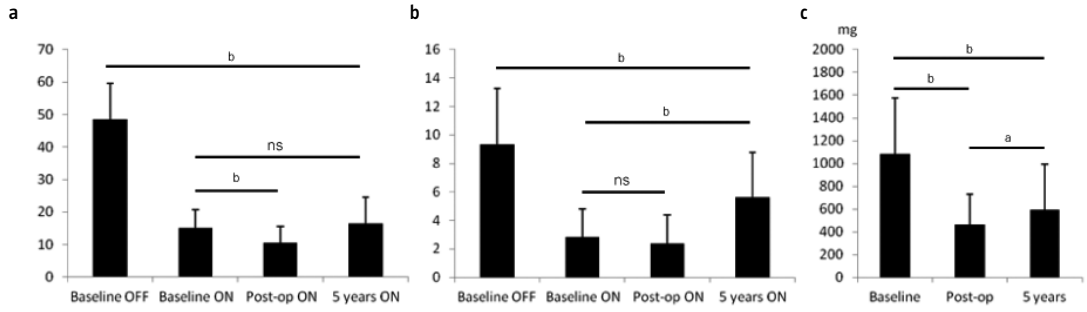

Table II. Modified Rankin Scale scores ($n = 59$).

Score	Baseline	1 month	5 years
0	0	0	0
1	1 (1.7%)	1 (1.7%)	0
2	45 (76.3%)	52 (88.1%)	30 (50.8%)
3	12 (20.3%)	6 (10.2%)	22 (37.3%)
4	1 (1.7%)	0	6 (10.2%)
5	0	0	1 (1.7%)
6	0	0	0

Compared to baseline 'off' state, motor function significantly improved by 78% 1 month after surgery (score: 10.6 ± 5.0; $p < 0.001$) and 66% at 5 years (score: 16.6 ± 8.0; $p < 0.001$). There was significant improvement 1 month after surgery, when compared to baseline 'on' state ($p < 0.001$), and there was no difference at 5 years when compared to the pre-operative 'on' assessment (Fig. 2).

With regard to axial symptoms the mean score before the procedure was 9.3 ± 4.0 in the 'off' state and 2.9 ± 1.9 in the best 'on', 2.4 ± 2.0 at 1 month after the surgery and 5.6 ± 3.2 after 5 years. Compared to baseline, axial symptoms improved postoperatively, but significantly worsened at 5 years (Fig. 2). There were no differences between preoperative and 1 month postoperative scores, but there was significant worsening at 5 years of follow up. However, the score remained significantly lower when compared to baseline ($p < 0.001$).

The mean LEDD decreased significantly after STN-DBS, from a daily dose of 1087 ± 489 mg/day at the baseline to 464 ± 263 mg/day at 1 month and 594 ± 397 mg/day at 5 years ($p < 0.001$). There was a slight but significant increase in the daily medication requirements from 1 month to 5 years ($p < 0.05$) (Fig. 2).

Disability (Table II)

Seven patients (12%) improved and 52 patients (88%) maintained their previous mRS score at 1 month ($p = 0.011$). At 5 years, 32 patients (54%) maintained the same score, 23 (39%) had worse scores and 4 (7%) had better scores, as compared to baseline. The increase in the mRS score was statistically significant at 5 years ($p < 0.001$). Nevertheless, the majority of patients (88%) was able to walk unassisted (mRS ≤ 3) at 5 years, with 6 patients presenting mRS of 4 (one was demented, one was wheelchair-bound following stroke, three severe osteoarticular disorders impairing gait and one had bilateral lower limb prosthesis following a failed suicide attempt), and 1 patient had a mRS score of 5 (dementia at 5 years).

Cognitive assessment

One patient (1.6%) at 6 months and 19 patients (32%) at 5 years met diagnostic criteria for dementia. The average age of the demented patients (63.7 ± 5.9 years) was significantly higher than that of non-demented patients (56.4 ± 8.0 years; $p < 0.001$). There was no difference in disease duration between both groups (14.8 ± 5.7 vs 13.5 ± 7.1; $p = 0.480$).

Discussion

This study describes the clinical outcomes and progression of PD patients undergoing bilateral STN-DBS at Centro Hospitalar São João (Porto, Portugal) up to 5 years after the procedure.

The results of the present study confirm that the beneficial effects gained from STN stimulation on levodopa responsive PD symptoms are preserved 5 years after the surgery. There was a significant improvement on both total and axial motor scores postoperatively, when compared to baseline. LEDD was also greatly reduced postoperatively. However, some of the clinical benefits of STN-DBS declined after 5 years of follow-up, although total motor scores remained significantly improved. The 66% motor improvement achieved at 5 years in this series, as well as the reduction of medication requirements, is in accordance with the results from other long term studies [4,7,10,12-15,25-27]. Motor improvement allowed for a mean 55% reduction of dopaminergic drugs. After the initial post-operative improvement, worsening of axial signs was observed at 5 years, although significant benefit was still detected when compared to baseline 'off'. Axial signs typically respond poorly to levodopa, and will also usually respond poorly to DBS [28]. The worsening of axial motor signs in the long-term follow-up has been found by other groups [4,7,11,14,15,25,29-31], which fits the expected course of PD [32,33]. This has been attributed to the extension of the pathological processes to non-dopaminergic neural systems and this evolution cannot be reversed by levodopa treatment or DBS [33-35]. Other groups have pointed out that axial signs seem to selectively deteriorate, considering that the global motor outcome remains improved. Gait deterioration not present before surgery that became apparent shortly after the procedure has been previously described [29] Additionally, in studies comparing STN and globus pallidus internus (GPi) stimulation, there was less worsening of axial symptoms in the latter group, suggesting a putative role of STN-DBS in this decline. However, the fact that GPi patients usually maintain high levodopa doses after surgery, unlike STN-DBS, must be taken into consideration [30] Nevertheless, there seems to be a benefit of STN-DBS on axial symptoms and the contribution of the procedure to its deterioration cannot be assessed in this study.

Disability was evaluated using the mRS. This is a validated measure of global disability and one of the major outcome measures in stroke clinical trials. Although it has not been validated for PD, the mRS has shown significant association with measures of motor and non-motor impairment, disability and quality of life in PD and has the potential to become a global measure of disability in this disease [36]. Despite a significant improvement in disability after STN-DBS, there was significant worsening 5 years after surgery. This worsening is in keeping with the decline in gait and other axial signs, which could be associated with this deterioration. Moreover, most patients presenting higher scores (mRS > 3) also presented additional comorbidities contributing to their status. Nonetheless, most patients in this series (88%) retained the ability to walk unassisted at 5 years, suggesting long-term benefit of STN-DBS in this regard. These results are consistent with the improvement in daily life activities and quality of life after DBS seen in other studies [3,4,10,11,13,14, 26,27].

In this series, there was a significant decline in cognition, 32% of the patients meeting the diagnostic criteria for dementia at 5 years after the procedure, one of whom during the first 6 months of follow-up. Similar rates of dementia have been reported by other groups, ranging from 28-47% with 2 to 5 years of follow-up [31,37,38]. However, other studies reported lower rates [4,15,39]. Some groups also have described early development of dementia following DBS, ranging from 4-10% within the first 3 to 6 months [4,37,38,40]. Dementia is a common occurrence in PD, developing typically a few years after the onset of motor symptoms [2,17]. The incidence of dementia is increased by 2.8 to 6-fold in those with PD when compared to those without the disease. Cognitive decline is noted in up to 36% of newly diagnosed cases of PD and at least 75% of the patients with PD who survive for more than 10 years will develop dementia [2,41].

Patients who eventually became demented during the follow-up period were significantly older than non-demented patients in this series, although disease duration did not seem to have a role, a finding also reported in other studies [37,41-44]. This relationship with age, independent of disease duration, suggests that additional neurodegenerative and/or vascular pathology may contribute to the emergence of dementia. Cognitive changes have been observed in elderly patients both with and without pre-existing cognitive impairment before surgery [45,46]. Thus, advanced age is a risk factor for cognitive deterioration after DBS, although it may be simply the result of the presence of other comorbidities, which could cause the threshold for manifestation of dementia to be crossed at an earlier stage. This could argue in favor of offering DBS ear-

lier in the course of disease, when DBS could have greater benefit on quality of life for patients with less advanced disease, with fewer risks of aggravating axial signs or triggering cognitive impairment. Accordingly, the results of the recently published EARLYSTIM trial support the use of STN-DBS earlier in the course of disease [47].

Of note, one patient (1.6%) presented with dementia 6 months after STN-DBS. Given the early deterioration, one could speculate on the role of the procedure itself on such an outcome, considering the effect of the STN in the processing of associative and limbic information towards cortical and subcortical regions [48] Also, the disruption of projections from the basal ganglia to the prefrontal cortex has been suggested as a cause for decreased verbal fluency after DBS and lesional surgery [49] Despite these findings, STN-DBS in PD seems generally safe from a cognitive standpoint [16].

In summary, in this series, STN-DBS was effective in controlling motor symptoms of PD, even five years after the procedure. Deterioration of axial symptoms and disability, as well as new onset dementia have been observed in this period, but the role of STN-DBS in this clinical progression cannot be defined due to the absence of a control group of medically treated patients with clinical features similar to those having DBS.

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Estimulación cerebral profunda del núcleo subtalámico en la enfermedad de Parkinson avanzada: seguimiento de cinco años en un centro portugués

Introducción. La estimulación cerebral profunda (ECP) del núcleo subtalámico (NST) en la enfermedad de Parkinson (EP) es segura y eficaz: en la mayoría de series se describen respuestas motoras duraderas y estables.

Objetivo. Informar sobre el desenlace a largo plazo de la ECP del NST en pacientes con EP avanzada atendidos en un centro hospitalario portugués.

Pacientes y métodos. El estado motor se valoró con la escala unificada de valoración de la enfermedad de Parkinson, parte III, antes de la intervención quirúrgica –en dos situaciones: sin efecto de la medicación (*off*) y bajo el mejor efecto (*on*)–, en el postoperatorio y al cabo de cinco años (medicación y estimulación en *on*). Se cuantificaron las puntuaciones de cada síntoma axial. La incapacidad se evaluó con la escala de Rankin modificada (mRS). La aparición de demencia se valoró seis meses y cinco años después de la ECP.

Resultados. Setenta y uno de los 183 pacientes sometidos a la ECP del NST concluyeron los cinco años de seguimiento. Diez de ellos quedaron excluidos: dos por fallecimiento (cáncer e infarto de miocardio), cinco por pérdida de seguimiento y tres por la retirada del sistema de estimulación. La función motora manifestó una mejora del 78% en el postoperatorio y del 66% a los cinco años. En el postoperatorio se apreció mejoría de los síntomas axiales, pero al cabo de los cinco años habían empeorado de manera significativa ($p < 0,001$). Las puntuaciones de la mRS también mejoraron en el postoperatorio, pero a los cinco años también habían disminuido, pese a que la mayoría (88,5%) conservaba la capacidad ambulatoria (mRS < 4). Un paciente (1,6%) manifestó demencia a los seis meses, mientras que otros 19 (31,2%) la manifestaron al cabo de los cinco años. La edad de los pacientes dementes era notablemente mayor (56,5 ± 7,8 frente a 63,7 ± 5,9 años; $p < 0,001$).

Conclusiones. En esta serie de casos, la ECP del NST demostró su eficacia en la mejora de los síntomas motores, aunque habían transcurrido cinco años desde la implantación. En ese período hubo un deterioro de los síntomas axiales y de la incapacidad, y surgieron casos de demencia, pero el posible papel de la ECP del NST como factor causal resta pendiente de concretar.

Palabras clave. Demencia. ECP. Enfermedad de Parkinson. Estimulación cerebral profunda. Incapacidad. Núcleo subtalámico. Seguimiento a largo plazo. Valoración motora.