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Key clinical milestones 15 years and onwards after DBS-STN surgery—A retrospective analysis of patients that underwent surgery between 1993 and 2001

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ABSTRACT

Objective: Subthalamic nucleus deep brain stimulation (STN-DBS) is an effective treatment for motor fluctuations in Parkinson's disease (PD), but does not halt disease progression. The long-term deterioration of key functions such as cognition, speech, ability to swallow, gait, urinary bladder control, orientation and reality perception is decisive for patients' independency in daily life. In this paper we investigated patients with advanced PD operated at our center with STN-DBS for at least 15 years ago, in respect to key clinical milestones reflecting their overall function in daily living.
Patients and methods: Retrospective analysis of clinical data concerning key clinical milestones including death in PD-patients, 15 years or more after they underwent STN-DBS surgery. All PD-patients implanted with STN-DBS at Sahlgrenska Hospital before January 1, 2001, were regularly assessed until death, drop-out, or January 11, 2016.
Results: Sixteen men and seven women with a median (range) disease duration of 18 (10–28) years were operated with STN-DBS. The median (range) follow-up time post-surgery was 12 (2–18) years and 692 person-years of disease duration were observed. In January 2016, nine PD-patients (39%) were still alive (eight with active STN-DBS). Initially, motor symptoms improved in all patients. Sustained benefit (implying active stimulation at the last follow up) was maintained in 19 of them (83%) but STN-DBS was inactivated in four (17%) due to inefficacy. Over time, all patients deteriorated slowly, and a majority developed severe non-motor and axial symptoms such as dementia, inability to talk, swallow and walk, urinary incontinence, psychosis, and need for nursing home care. At the last follow up, 16/23 (70%) patients were treated with antidepressants.
Conclusion: A majority of PD-patients experience sustained motor benefit with continuous STN-DBS. However, over time, non-motor and axial symptoms slowly and severely restrict PD-patients' function in their daily living.

1. Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is an efficacious treatment for selected individuals with advanced Parkinson's disease (PD) suffering from suboptimal motor control and motor fluctuations despite optimal peroral medication. After successful surgery, STN-DBS improves both motor and some non-motor symptoms and makes possible a reduction of the total dopaminergic medication load [1] thereby reducing pharmacological side effects [2,3]. However, over the years, the underlying disease processes continue unabated and lead to deterioration of non-motor and axial motor functions. In addition, there have been observations that STN-DBS may adversely impact cognition and other neuropsychiatric features [4] The longest previously reported follow-up time after STN-DBS is 10 years, at which time axial and non-motor symptoms cause a significant functional impairment

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despite the fact that many motor symptoms are still reasonably treatment responsive [5–7]. In a study of 19 PD-patients treated with STN-DBS after an average of 23 years disease duration, and followed up for up to 30 years after disease onset and 5 years after DBS-surgery (in a subgroup up to a mean of 8.42 years), 43% developed dementia, 86% dysphagia, 57% urinary incontinence, and 64% falls [8]. This may simply reflect the known fact that in PD, disease duration is associated with progressive disability, as shown in other studies. Thus, after 15 years of disease, 48% of medically treated PD-patients had developed dementia, 36% had mild cognitive impairment, 50% had psychotic symptoms, 50% choked occasionally, and 27% had a severe speech impediment and were often unintelligible; 41% had urinary incontinence and 40% had to live in nursing homes [9]. A current trend is to introduce STN-DBS at earlier disease stages hoping to prolong the time with good symptom control and to postpone dependency [10]. A better understanding of long-term outcomes, after more than 10 years post-surgery, is therefore important.

In this study we review key clinical milestones in PD-patients operated with STN-DBS 15 years ago or more, for the treatment of advanced motor fluctuations.

The Neurology Department, Sahlgrenska University Hospital, Göteborg, Sweden, was one of the early adopters of STN-DBS for advanced PD. More than 20 PD-patients were operated at the turn of the millennium, when STN was still a novel target, and patient selection criteria were under development [11]. In this study we report a follow-up of all our PD-patients operated in this early period (before STN-DBS was FDA approved) in respect to key clinical milestones reflecting their overall function in daily living.

2. Patients and methods

Retrospective analysis of demographical, clinical and STN-DBS data from subjects with advanced PD implanted with STN-DBS systems before January 1, 2001, at our center. Data was retrieved from clinical files and was based on examinations and interviews, conducted by movement disorders specialist, other physicians, nurses, physiotherapists, occupational therapists, social workers and psychologists. All reported data from the last follow-up refers to data obtained at the last recorded visit, with patients in their best ON-phase, with both medication and stimulation ON. The STN-DBS status was recorded as ON (active) or OFF (inactive), together with a motivation if stimulation was OFF. The presence of key clinical milestones and their date of onset were recorded. The chosen key clinical milestones reflecting the overall function of the PD-patients in daily living were the occurrence of: (1) dementia (defined as a score of 4 on Unified Parkinson's Disease Rating Scale [UPDRS] 1.1 [12]); (2) inability to talk (a score of 4 on UPDRS 3.1); (3) inability to swallow [need for percutaneous endoscopic gastrostomy (PEG)]; (4) inability to walk [H&Y stage 5 (need for wheelchair)]; (5) development of urinary incontinence [score 4 on UPDRS 1.10 (need for protective garments, chronic or intermittent catheterization)]; (6) development of psychosis [a score of 3 or 4 on UPDRS 1.2 (formed hallucinations with loss of insight and/or delusions)]; (7) loss of autonomy (need for nursing home or personal assistant 24 h a day, every day). The total levodopa equivalent dose (TLED) was calculated as previously reported [13], as well as the number of groups of antiparkinsonian drugs used [levodopa (including levodopa-carbidopa intestinal gel), agonists (including apomorphine), COMT-inhibitors, MAO-B inhibitors, and amantadine]. Use of antidepressants, acetylcholinesterase inhibitors and antipsychotics was recorded. Information about the date and cause of death was obtained from the Swedish Mortality Registry.

STN-DBS treatment was considered to be inefficacious when it did not improve disease parameters (objectively, as deemed by the medical staff after tests and interviews, and subjectively, as deemed by the patient) compared with PD-medication alone, or when stimulation caused significant and inacceptable side effects. Inefficacious STN-DBS was documented during planned efficacy assessments by turning off stimulation or when stimulation was found to be accidentally OFF and patients did not improve significantly when it was turned ON.

This study was approved by the Regional Ethical Board in Gothenburg, Sweden.

Descriptive statistics were used to present the results, when appropriate. Values are expressed as median (range), unless otherwise specified. Survival statistics including Kaplan–Meier graphs and Log Rank analyses were used to investigate symptom development over time. Related-samples Wilcoxon Signed Rank Test was used for comparing TLED at baseline (before STN-DBS) and at the last recorded visit. Analyses were performed in all PD-patients, and separately for males and females, and for those with PD onset before and after the age of 50 years. Significance was chosen at $p < 0.05$.

3. Results

3.1. Demographics and PD related clinical scores

Twenty-three PD-patients (16 males and 7 females) were implanted with STN-DBS systems between December 1993 and January 1, 2001. At the time for surgery their age was 60 (48–71) [median (range)] years, their PD duration 18 (10–28) years, Schwab & England score 70 (50–90), and Hoehn & Yahr stage 3 (2.5–4) [14]. Their age at PD onset was 40 (30–71) years. Following surgery, motor function improved in all patients. At the last follow-up, all PD-patients were significantly worse compared with baseline (preoperatively), with a Hoehn & Yahr stage of 5 (2.5–5) and a Schwab & England score of 25 (10–75) ($p < 0{,}001$). The median PD duration at the last follow-up was 30 (16–40) years. The total PD observation time (from disease onset) for the entire cohort was 692 person-years.

3.2. Follow-up

All patients were regularly followed up at our center after operation. Eighteen patients remained at our center for the entire follow up (six still alive and 12 dead) while five moved to other areas and were followed up there. For the purpose of this study, their clinical data is collected as recorded at the last available visit at our center. After that, they are considered lost to follow-up, except for information regarding survival as of January 11, 2016. Overall, the median follow-up time at the last visit was 12 (2–18) years and the total observation time post STN-DBS was 256 person-years. Detailed information regarding follow-up time and age at death (when applicable) for all patients is presented in Supplementary Table 1.

3.3. Mortality

As of January 11, 2016, that is at least 15 years postoperatively, nine PD-patients were still alive (eight with the DBS ON) and 14 were dead (11 of them had the DBS ON at death). The first recorded death was less than 3 years postoperatively due to suicide. See Fig. 1(a) for survival after STN-DBS surgery and 1(b) for survival after onset of PD.

3.4. STN-DBS status

Nineteen PD-patients continued to be treated with active STN-DBS for the entire duration of the follow-up, as it was considered by patients, caregivers and medical staff to be beneficial in respect