Parkinson's Disease
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Chapter 6

Presurgical FDOPA-PET and motor outcome of subthalamic nucleus stimulation in Parkinson’s Disease

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Submitted
Abstract

Objective: to predict the efficacy of STN-DBS on motor disability by quantification of the presurgical presynaptic striatal dopaminergic function in a selected population of levodopa responsive PD patients.

Methods: motor improvement after STN-DBS was analysed in a series of 19 patients with advanced PD at 12 and 24 months after surgery, and motor scores were related to presurgical putamen FDOPA-PET data.

Results: motor scores after STN-DBS were negatively correlated to presurgical FDOPA-PET data.

Conclusion: FDOPA-PET is not a meaningful predictor of surgical outcome of STN-DBS. Our study data might support the hypothesis that the efficacy of STN-DBS on motor symptoms in PD is modulated at the poststriatal level and downstream within the basal ganglia circuitry.
Introduction

Idiopathic Parkinson’s disease (PD) is a progressive, neurodegenerative disease, which is clinically characterised by an asymmetric onset of bradykinesia, rigidity and resting tremor\(^1\). Current drug therapy in PD is symptomatic and primarily aimed at restoring dopaminergic function in the striatum, and levodopa remains the most effective treatment\(^2\). However, its long-term use is associated with the inevitable development of motor fluctuations and dyskinesia despite optimisation of pharmacological treatment\(^3\).

A selected population of PD patients with severe motor complications are suitable candidates for surgical intervention, especially Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN)\(^4\). Several longitudinal studies have shown a convincing improvement in almost all cardinal motor features of PD by chronic bilateral STN-DBS\(^5-8\).

It is assumed that patients’ preoperative dopamine responsiveness predicts the clinical efficacy of STN-DBS. However, not all PD patients benefit equally from surgery, and thus far only few studies have attempted to assess additional clinical predictive factors of successful STN-DBS\(^9-12\). In this study we related the efficacy of STN-DBS on motor disability to the presurgical presynaptic striatal dopaminergic function, by means of 18-Fluorodopa Positron Emission Tomography (FDOPA-PET) and levodopa responsiveness, in a selected population of PD patients.
Methods

Patients
During a 4-year period 20 PD patients, 10 women and 10 men, were selected by one of the investigators at our outpatients’ Movement Disorder Unit and initially included in the study. All patients suffered from severe motor fluctuations and dyskinesia and were therefore selected for chronic bilateral STN-DBS. 1 female patient (age 52 years, disease duration 18 years) was retrospectively excluded from the study because she only had 1 DBS electrode positioned (due to surgical complications), although she completed the clinical follow up. Their mean age (n = 19) was 61 ± 8 years, and all patients showed preserved levodopa responsiveness with a substantial improvement (mean 23 ± 9, range 8-40) on the Unified Parkinson’s Disease Rating Scale (UPDRS) part III score. All patients were treated with levodopa (and a peripheral decarboxylase inhibitor) and dopamine agonists. For additional patient characteristics see Table 1.

Additional inclusion criteria for surgery, according to the CAPSIT-PD protocol, were: no depression (Montgomery and Asberg Depression Rating Scale, score < 19) nor dementia (Mattis Dementia Rating Scale, score > 130), no abnormalities on cerebral MRI, and no recent psychiatric illness nor restricted physical condition for surgery. This study was approved by the hospital ethics committee and all patients gave their informed consent prior to study inclusion.

Clinical evaluation
Patients were evaluated clinically at baseline (3 - 6 months before planned surgery), 12 months (n = 19) and 24 months (n = 8) after STN-DBS. Antiparkinsonian medication was kept unchanged during a period of 2 weeks prior to all assessments. The patients’ motor status was obtained using the UPDRS part III in off- (after withdrawal of all parkinsonian medication overnight) and on- (1 ½ hour after regular, postponed, early morning levodopa dosage) medication condition. Postoperatively the UPDRS part III was assessed in the on-stimulation condition.

Surgery
Before surgery all antiparkinsonian medication was withdrawn overnight. All patients had surgery in the supine position by the same neurosurgeon (MJS). A 3D-volume T1 weighted MRI scan (Siemens Sonata Vision, 1 ½ Tesla) was performed with the Leksell G frame in place, generating 2 mm-slices, which were transferred subsequently into a computerised planning system (@TargetBrainLAB). These images were then fused with a preoperative MRI T2-weighted scan and after depiction of the AC-PC line the STN Talairach coordinates were determined by direct visualisation of the STN in anatomical reference to well known anatomical landmarks. The targeting was completed using semi-micro electrode (SME) recording in combination with macro-stimulation and assessment of the clinical effect. Finally, the SME was replaced by a quadripolar lead (Medtronic, Minneapolis, MN; type 3389, containing 4 electrode contacts over a length of 7,5 mm) on both sides. Postoperatively the position of the lead
was verified by skull X-ray and T2-weighted MRI, and additionally the MRI images were fused with the target planning MRI. After surgery the patients’ peroperative clinical response was reproduced through external STN-stimulation. One week later the programmable pulse generator (Kinetra, Medtronic) was implanted in a subclavicular subcutaneous pocket and connected with the DBS leads by two extension wires. Finally, dopaminergic therapy and DBS stimulation parameters were gradually adjusted by the investigators based on the patients’ best clinical response.

**PET data acquisition and analysis**

All PET measurements were performed at the UMC PET Center on a Siemens ECAT 951 (n = 8; 6 men, 2 women) or Exact HR + (n = 11; 3 men, 8 women) scanner in a 2D-mode. In each patient a single FDOPA-PET scan was undertaken 4 ± 3 months (range: 1 - 10) prior to STN electrode implantation. Subjects were positioned supine in a resting state with their eyes closed and ears unplugged. After pre-treatment with 2 mg/kg carbidopa orally to block peripheral dopamine decarboxylase activity, 185 ± 31 MBq FDOPA was injected intravenously over 1 minute with an infusion pump. All subjects were measured following a static or dynamic scanning protocol with identical time range for data analysis. The static protocol consisted of 1 single scan from 90-120 minutes post-injection. The dynamic protocol consisted of 21 time frames with increasing duration over a period of 120 minutes; then the last 2 frames (2 x 900 sec) were averaged to create a volume equivalent to the static protocol. Linear normalisation with SPM99 \(^\text{15}\) was used to align the measured volume data to a rCBF template fixed in Talairach co-ordinate space \(^\text{16}\). Region of interest (ROI) analysis was based on a standardised template fixed in Talairach coordinate space. This template, consisting of 6 regions of interest (ROI) (putamen, caudate, and occipital lobe on both sides) was used to sample the volume data and compute mean ROI activity concentration. Specific FDOPA uptake was expressed as a striato-occipital ratio (SOR)-index following the equation: $\text{SOR-index} = \frac{C_{ROI} - C_{REF}}{C_{REF}}$ ($C_{ROI}$ = average (left and right) ROI activity concentration, $C_{REF}$ = average occipital activity in the occipital reference region).

**Clinical and statistical data analysis**

The surgical efficacy of STN-DBS, e.g. the postoperative clinical response to stimulation, was calculated as: improvement from stimulation = preoperative UPDRS part III score (off-medication) – postoperative UPDRS part III score (off-medication / on-stimulation) \(^\text{9}\). The presurgical motor response to levodopa was calculated as: improvement from levodopa = preoperative UPDRS part III score (off-medication) - preoperative UPDRS part III score (on-medication). Spearman’s nonparametric rank correlation ($\rho$) was used to determine predictors of clinical outcome after surgery (SPSS for Windows 10.0, SPSS UK Ltd, Surrey, England) and a p-value of < 0.05 was considered to indicate statistical significance.
## Table 1  Patient characteristics

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* At study inclusion
+ In off-medication condition
# Presurgical motor response to levodopa (see data analysis)
& LEDD (Levodopa Equivalent Daily Dose) = levodopa dose (100 mg) x 1 (added with 0.2 x levodopa dose if using entacapone with each dose) + (slow release levodopa x 0.7) + bromocriptine x 10 + ropinirole x 20 + pergolide x 100 + pramipexole x 100
Chapter 6

Results

All study patients completed clinical follow-up at 12 months, and additionally 8 patients were also assessed 24 months after surgery. They all underwent uncomplicated surgery, while 2 patients suffered from transient confusion direct postoperatively. The best clinical results 12 and 24 months after STN-DBS were achieved by bilateral monopolar (n = 15), bipolar (1) or monopolar / bipolar (n = 3) stimulation. The median frequency of stimulation was 135 Hz, the pulse width 60 µsec, and the mean voltage $2.72 \pm 0.74$ V (12 months) and $2.54 \pm 0.52$ V (24 months). STN-DBS resulted in a considerable decrease in motor disability 12 and 24 months after surgery (mean reduction in UPDRS part III off-medication score: $20 \pm 9$ (n = 11, range: 2 – 35) and $23 \pm 8$ (n = 8, 14 - 35). The mean putamen FDOPA-uptake was $0.58 \pm 0.21$ (range: 0.27 - 0.98). Negative correlations were found between presurgical putamen FDOPA uptake and the surgical outcome at 12 (n = 19, $\rho = -0.485$, p = 0.049) (see figure 1) and 24 months after surgery (n = 8, $\rho = -0.712$, p = 0.048). No significant correlations were found between the surgical outcome and presurgical motor response to levodopa at 12 ($\rho = 0.062$, p = 0.8) and 24 ($\rho = 0.38$, p = 0.35) months after STN-DBS, nor between presurgical putamen FDOPA uptake and presurgical levodopa responsiveness ($\rho = -0.38$ and p = 0.88 respectively).

Discussion

This is the first study aimed at providing a non clinical predictor of the motor efficacy of STN-DBS in advanced PD by means of assessment of the presurgical nigrostriatal dopaminergic status in individual patients. Thus far only one indirect measure of striatal dopamine integrity (levodopa responsiveness) has been used as an important clinical predictor of surgical efficacy, and reports thus far showed an excellent outcome of STN-DBS in levodopa-responsive forms of PD\(^{10,12}\). However, additional clinical patient characteristics have been less predictive or study results seem conflicting, and further individual data on “non-responders” are mostly lacking\(^9,12\).

Our study confirms the long term efficacy of STN-DBS in levodopa responsive PD, and the postsurgical reduction in motor disability equals those stated previously\(^7,8\). The mean putamen FDOPA uptake in our study population was 34 % of healthy controls, and individual uptake ratios were in the range of values of PD patients with an advanced nigrostriatal dopaminergic deficit\(^17\). The presurgical nigrostriatal integrity in our patient population, as assessed by putamen FDOPA-PET, was negatively correlated to the achieved surgical efficacy of STN-DBS at clinical follow-up. This finding is somewhat counterintuitive. However, it can be argued that the more severely lesioned nigrostriatal dopaminergic system leaves more “room” for clinical improvement if by way of STN-DBS alternative neuronal networks can be activated or inhibited, in order to circumvent the deleterious influence of the nigrostriatal dopaminergic lesion.
Since a low putaminal FDOPA uptake reflects a high presynaptic enzymatic nigrostriatal deficit, our data might reflect the hypothesis that the efficacy of STN-DBS on motor symptoms in PD is mainly achieved at the poststriatal level. In addition, it is suggested that STN-DBS may work only or mainly downstream within the basal ganglia simply by altering or blocking the transmission of pathological information to the thalamocortical and brainstem motor area. This hypothesis is further supported by recent studies demonstrating that the main mechanism of action of STN-DBS seems not related to an increased dopamine release by modulation of dopaminergic activity. In addition, we recently finished a study on PD disease progression after STN-DBS using serial FDOPA-PET, and demonstrated a continuing and ongoing decline of dopaminergic function in PD after successful surgery (personal communication). Although in our study a negative correlation was found between preoperative FDOPA uptake and surgical outcome, this association is too weak to predict meaningfully preoperatively the outcome of STN surgery. In addition, accurate placement of DBS electrodes and adjustment of DBS stimulation parameters optimise clinical improvement and remain important critical factors to obtain maximum benefit of stereotactic surgery.

Figure 1. Mean putamen FDOPA uptake and motor improvement 12 months after STN-DBS.

Case numbers correspond to patient numbers used in table 1.
Broken lines indicate mean regression prediction line and 95% confidence interval.

Mean putamen FDOPA-PET control values (UMC, Groningen):
- healthy volunteers (56 ± 19 years, n = 10): 1.69 ± 0.29
- PD patients (64 ± 6 years, disease duration 9 ± 3 years, n = 18): 0.79 ± 0.10
In conclusion, FDOPA-PET is not a meaningful predictor of surgical outcome of STN-DBS, and our data might support the hypothesis that the efficacy of STN-DBS on motor symptoms in PD is modulated at a level downstream within the basal ganglia circuitry.

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References


