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Short communication

Long-term evaluation of impedance levels and clinical development in subthalamic deep brain stimulation for Parkinson's disease

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ABSTRACT

Background: This study was conducted to better understand the development of clinical efficacy and impedance levels in the long-term course of deep brain stimulation (DBS) of the subthalamic nucleus (STN) in Parkinson's disease (PD).
Methods: In this retrospective study of twenty PD patients, the motor part of the Unified Parkinson's Disease Rating Scale was periodically assessed i) after withdrawal of medication and inactivated stimulation, ii) after withdrawal of medication with activated stimulation and iii) after challenge with L-Dopa during activated stimulation up to 13 years after surgery.
Results: STN-DBS with or without medication significantly improved motor function up to 13 years after surgery. The contribution of axial symptoms increased over time. While the stimulation parameters were kept constant, the therapeutic impedances progressively declined.
Conclusion: STN-DBS in PD remains effective in the long-term course of the disease. Constant current stimulation might be preferable over voltage-controlled stimulation, as it would alleviate the impact of impedance changes on the volume of tissue activated.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective therapy for patients with Parkinson's disease (PD) [1]. In particular, chronic high frequency STN-DBS reduces motor fluctuations apart from a general improvement of tremor, bradykinesia, and rigidity. Despite the fact that many studies demonstrated the efficacy of STN-DBS in PD patients during the first years after surgery, including the temporary reduction of dopaminergic medication and improvement of overall quality of life, only a few studies analyzed its effects after more than a decade [2–4]. Besides, less is known about the long-term development of impedance levels. Changes of impedance however have been shown to influence the shape of the volume of tissue activated by DBS [5], which in turn may have an impact of the clinical efficacy of the treatment. Thus, the aim of the current study was to elucidate the clinical and technical course of STN-DBS in 20 patients during a clinical follow-up period of up to 13 years.

2. Patients and methods

2.1. Patient selection and investigation

From 111 PD patients who were implanted in our center for STN-DBS between 1998 and 2003, 20 patients completed regular follow-up and were accepted for further retrospective analysis. A detailed overview of the selection process and pertinent patient data is provided as supplementary material. The study was approved by the local ethics committee (study number 4640).

Prior to surgery, the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was assessed after withdrawal of dopaminergic medication for at least 12 h (Med-OFF) and after a challenge with 200–300 mg soluble L-Dopa (Med-ON). After surgery, all patients underwent regular clinical follow-up visits.

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Therapeutic impedances were obtained and the UPDRS-III was video-documented and evaluated for the following conditions: i) after withdrawal of any dopaminergic medication for at least 12 h but ongoing STN-DBS (Med-OFF/Stim-ON), ii) after inactivation of STN-DBS for 1–2 h and still withdrawn medication (Med-OFF/Stim-OFF), iii) 1 h after a challenge with 200–300 mg soluble L-Dopa and reactivation of STN-DBS (Med-ON/Stim-ON). Besides the total sum of the UPDRS-III, items of appendicular motor signs (items 20–26, and 31) and sub scores of axial symptoms (items 18, 19, and 27–30) were independently investigated.

2.2. Statistics

For statistical analysis, the UPDRS-III scores were allocated to 8 different time clusters: The first cluster consisted of the preoperative assessment of motor function and will be termed baseline (BL) value in the following. The second one represented the UPDRS-III score within the first year after DBS surgery (‘1’). The remaining clusters represent the average scores of two subsequent years (‘2–3’, ‘4–5’, ‘6–7’, ‘8–9’, ‘10–11’, and ‘12–13’, respectively). If a cluster consisted of just one but not two different UPDRS-III scores, this single score was exclusively used as cluster value. Additionally, the applied levodopa equivalent dosage (LEDD) was calculated for each cluster according to recommendations by Tomlinson et al. [6]. Statistical analyses were performed with R (Version 3.02) employing the ‘nlme’- and ‘multcomp’-package. All datasets presented a parametric distribution, as investigated with the Kolmogorov–Smirnov test. For the UPDRS-III and its sub items, regression analyses were performed on the mean values of each time cluster and for each treatment condition. The same approach was used to explore changes of the stimulation settings over time. A mixed linear model accounting for repeated measures followed by post-hoc analysis based on Tukey's approach for multiple comparisons was utilized to compare postsurgical LEDD and the UPDRS-III values obtained in each time cluster.

3. Results

3.1. L-dopa equivalent daily dosage (LEDD), DBS setup and impedance measurements

Linear regression analysis of mean impedance measurements showed a progressive decrease over time (21 Ohm per year, $R^2 = 0.95$). A summary of the results is provided in Fig. 1; further information on the individual course of impedance levels can be found in the supplementary material. The setup of voltage, pulse width, and stimulation frequency (averaged for both hemispheres) did not significantly change over time. The LEDD significantly decreased by more than 50% in the first year of DBS ($p < 0.001$) and by more than 25% in the following cluster 2–3 years after surgery ($p < 0.01$), compared to BL values. Subsequently, the LEDD returned to higher amounts which did not differ significantly from BL values.

3.1.1. Assessment of the total UPDRS-III score

Linear regression analysis of the mean UPDRS values for each time point confirmed almost identical slope of the regression lines for Med-OFF/Stim-ON (1.4/year, R^2; = 0.96) and Med-ON/Stim-ON (1.3/year, $R^2 = 0.98$), which were steeper compared to Med-OFF/Stim-OFF (0.3/year, $R^2 = 0.59$). For all time clusters, the total UPDRS-III score of Med-OFF/Stim-ON and Med-ON/Stim-ON were significantly lower than Med-OFF/Stim-Off (Fig. 2A).

3.1.2. Assessment of the UPDRS-III subscales

Appendicular motor signs did not significantly change over time in the Med-OFF/Stim-OFF condition, as indicated by a slope of the regression line that did not significantly differ from zero. In contrast, regression analysis of Med-OFF/Stim-ON and Med-ON/Stim-ON revealed a progressive decline (0.7/year for Med-OFF/Stim-ON ($R^2 = 0.96$) and 0.5/year for Med-ON/Stim-ON ($R^2 = 0.88$)) over time. Almost identical to the UPDRS-III total score, the appendicular motor signs of Med-OFF/Stim-ON and Med-ON/Stim-ON were significantly lower than Med-OFF/Stim-Off (Fig. 2B).

Sub scores of axial symptoms revealed a nonlinear relationship

		BL	1	2-3	4-5	6-7	8-9	10-11	12-13
LEDD (mg)		1018 (445)	459 (356)***	714 (390)**	825 (400)	811 (395)	876 (381)	828 (342)	807 (232)
Amplitude (V)		-	3.1 (0.7)	3.3 (0.6)	3.1 (0.6)	3.2 (0.7)	3.1 (0.8)	3.1 (0.7)	3.1 (0.6)
Pulse width (µs)		-	70 (18)	80 (23)	77 (22)	73 (19)	71 (16)	69 (14)	70 (14)
Frequency (Hz)		-	148 (24)	150 (23)	150 (23)	145 (23)	141 (20)	141 (20)	145 (23)
Contacts	(left)	-	1BP, 2MC	1BP, 1MC	1BP, 1MC	1BP, 1MC	1BP, 1MC	1BP, 1MC	1BP, 1MC
	(right)		2BP, 1MC	2BP, 1MC	2BP, 1MC	2BP, 1MC	2BP, 1MC	2BP, 1MC	2BP, 1MC
Impedance (Ω)		-	1036 (235)	953 (183)	892 (150)	879 (150)	815(193)	786 (133)	771 (177)

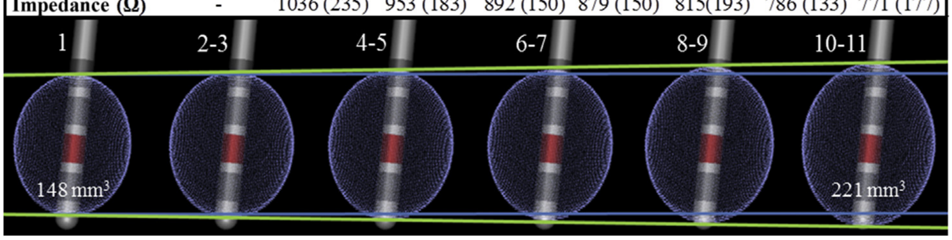

Fig. 1. Characteristics of the L-dopa equivalent daily dosage (LEDD) and stimulation settings over time as averaged data for both hemispheres (means, and standard deviations in brackets). Within the first three years after DBS surgery, the LEDD was significantly lower than prior to surgery (** indicates $p < 0.01$, *** indicates $p < 0.001$). No significant change was observed for the dynamics of the stimulation amplitude, pulse width, and stimulation frequency. Among the 40 contact selections for chronic DBS (one for each patient's hemisphere), three were set to a bipolar stimulation (BP). Three setups in the first and two setups after the first year of DBS employed multiple contacts (MC) as cathodes. Regression analysis indicated a continuous decline of impedance ($R^2 = 0.95$). The bottom part illustrates the development of the volume of tissue activated (blue dotted shade) in a homogeneous isotropic medium if monopolar cathodic stimulation is applied via the second lowermost contact (red color) with stimulation settings provided above. The calculation was performed as previously described, accounting for the electrode capacitance an encapsulation layer around the electrode [7]. A power function was used for regression analysis of the data provided by Butson et al. to approximate the impact of impedance values [5]. Within 10 years, the volume increases from 114 mm^3 to 221 mm^3. The green lines demonstrate the continuous enlargement of diameter along the z-axis, compared to constant values (as shown by the blue lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)