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*Original Investigation*

Characterizing the Intraoperative Microelectrode Recording-Induced Microlesion Effect on Motor Symptoms in Patients with Parkinson's Disease Undergoing Deep Brain Stimulation of the Subthalamic Nucleus

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Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment in patients with Parkinson's disease (PD) (5,8,13). DBS can be performed with or without intraoperative microelectrode recording (MER) (9-11,14). MER can be accompanied by spontaneous improvement of parkinsonian motor symptoms, referred to as the microlesion effect (MLE) (3). Although this phenomenon is widely recognized, its quantitative impact on motor symptoms is unknown. In this prospective study,

the MLE on motor symptoms and its correlation with the preoperative levodopa response (LR) was investigated in 30 patients with PD who underwent DBS of the STN.

MATERIAL and METHODS

Between August 2013 and July 2016, 65 patients with PD were referred to our center for DBS and 30 were found suitable for surgery. All patients underwent surgery at the Ondokuz Mayıs University (OMU) DBS Center.

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Preoperative Examination

In all patients, tremor, rigidity, and bradykinesia were assessed according to the Unified Parkinson's Disease Rating Scale (UPDRS) part III (6) score in the preoperative off-state.

Surgical Process and Intraoperative Examination

Antiparkinsonian drugs were discontinued 12 hours prior to the surgery. All patients underwent preoperative magnetic resonance imaging (MRI) scanning, consisting of 1-mm T1 axial images, with and without gadolinium, and 2-mm T2 axial images (Siemens, 3-Tesla MR scanner, Erlangen, Germany). The STN was visualized by direct targeting using T2W MRI and the trajectory was planned. The number of MER electrodes used depended on the vasculature visualized using T1W MRI with gadolinium enhancement (Framelink 5, Medtronic Inc. Minneapolis, USA). The Leksell G frame was mounted and a stereotactic computerized tomography (CT) was performed without contrast and with a slice thickness of 1 mm (Aquillon 16 CT scanner, Toshiba, Tokyo, Japan) on the day of surgery. Following MRI-CT image fusion to calculate stereotactic coordinates, DBS surgery was initiated under local anesthesia for optimal MER and neurological examination. A precoronal burr hole was made on the most affected site. MER was performed using polyamide-coated tungsten microelectrodes (Medtronic; microelectrode 291; 10- μ m width, impedance 1.1 ± 0.4 M Ω ; measured at 220 Hz) in 1-mm steps from 10 mm above the target for the first 5 mm and there after in 0.5 mm steps until the termination of STN activity and initiation of substantia nigra pars reticulata (SNr) activity. Signals were recorded using the Lead Point System (Medtronic, Minneapolis, USA). The STN has a typical electrophysiological activity comprising high-voltage spikes, cells firing in the burst mode, and an obvious widening of the background. Before performing test stimulation using the same electrodes, patients were examined by the neurologist and baseline values for the tremor, rigidity, and bradykinesia were obtained according to the UPDRS part III scores. The microelectrode with the most typical STN pattern over the longest distance was always selected first for test stimulation. On achieving positive clinical results using lower stimulation amplitude with side effects being absent or only present at higher amplitudes, the microelectrode was withdrawn and replaced by a permanent lead (Model 3389; Medtronic, Minneapolis, USA). On achieving unsatisfying effects during test stimulation, another trajectory was chosen for clinical evaluation. The same procedure was performed on the contralateral side. MRI was performed to evaluate the position of the permanent leads and detect asymptomatic bleeding or other structural complications, following which the pulse generator (Activa PC; Medtronic, Minneapolis, USA) was placed under general anesthesia.

Calculation of MLE

MER-induced MLE was calculated based on the difference in tremor, rigidity, and bradykinesia scores between the preoperative off-state and the intra-operative state following MER and before test stimulation.

Statistical Analysis

Data are presented as mean \pm SD. The SPSS Version 15.0 was used for statistical analysis. The data observed was abnormally distributed, and therefore, between-group differences were analyzed non-parametrically. The Wilcoxon signed ranks test was used to compare the motor scores in the preoperative off-state and the period after IM. The correlations between LR, age, and disease duration with the MLE were investigated using Spearman rho correlation test. $p < 0.05$ was considered statistically significant.

RESULTS

Patients who underwent DBS of the STN and their corresponding mean age, sex distribution, disease duration, dominant extremity, and number of microelectrodes used during the operations are presented in Table I. We implanted 59 permanent leads, and 171 microelectrodes were used for MER throughout all surgeries. Approximately 2.8 microelectrodes were used to record each STN.

Comparisons of preoperative and intra-operative scores following MER are presented in Table II. A significant difference was observed in all motor subscores, in both upper extremities, attributable to MLE ($p < 0.05$). Tremor scores improved by 31.5% [left (L) side] and by 14.2% [right (R) side] ($p < 0.05$), rigidity scores improved by 17.3% (L) and 14.2% (R) ($p < 0.05$) and bradykinesia scores improved by 20.6% (L) and 11.5% (R) ($p < 0.05$). Total MLE scores improved by 21.7% (L) and by 13.6% (R) ($p < 0.05$). MLE was more pronounced for tremor and bradykinesia, compared to rigidity.

Although the total MLE was higher in patients with higher LR rate, no correlation was observed between these two parameters ($p > 0.05$). Similarly, there was no relationship between the total MLE and age or disease duration ($p > 0.05$). Moreover, no significant difference was found between MLE and the number of microelectrodes used ($p > 0.05$).

DISCUSSION

The present study demonstrates that substantial MLE occurs following MER. In the literature, discussions on the mechanisms of MLE are limited and include those on perifocal edema, metabolic change, and local immunological reactions within the tissue around the electrode (7,15,16).

Sitburana et al. have investigated MLE on essential tremor in patients with PD who underwent DBS of the thalamic ventral intermediate nucleus without MER (15). They had assessed solely the tremor response of MLE preoperatively, at 24-hour post-operatively, at initial activation, and at the 6-month follow-up. In their study, three quarters of patients had a moderate-to-marked MLE. They concluded that MLE had minimal long-term clinical effects, except for allowing for lower DBS settings (patients with a marked MLE had mildly lower DBS parameters). In another study, Tykocki et al. have evaluated the MLE in patients with PD who underwent DBS of the STN (17). They used 2–5 microelectrodes for MER on each side. Authors assessed the UPDRS-III motor score preoperatively,

Table I: Preoperative Data and the Number of the Used Microelectrodes

Number of Patients	Age (years)	Sex	Disease duration (year)	Levodopa Response (LR) (%)	Dominant extremity	Number of Microelectrodes
30	53 ± 9	M: 19 (63%) F: 11 (37%)	8.8 ± 2.8	55 ± 15	R: 11 (37%) L: 19 (63%)	R: 2.9 ± 1.2 L: 2.7 ± 1.1

Table II: The Comparison of Preoperative and Intraoperative Post-MER Motor Scores

	Left TS	Right TS	Left BS	Right BS	Left RS	Right RS	Left Total Score	Right Total Score
Preop Med-off Scores	1.9 ± 1.3	2.1 ± 0.8	2.9 ± 0.8	2.6 ± 0.7	2.3 ± 1	2.1 ± 0.8	2.3 ± 0.5	2.2 ± 0.2
Post-MER Scores	1.3 ± 1.2	1.8 ± 0.9	2.3 ± 0.8	2.3 ± 0.7	1.9 ± 1	1.8 ± 0.9	1.8 ± 0.5	1.9 ± 0.2
Improvement %	31.5	14.2	20.6	11.5	17.3	14.2	21.7	13.6
p	0.001	0.004	0.00	0.02	0.02	0.004	0.00	0.002

TS: Tremor score, **BS:** Bradykinesia score, **RS:** Rigidity score

within 48 hours of electrode implantation, and at the 6-month follow-up. They found MLE in the early postoperative period and observed a positive correlation between MLE and the degree of improvement with active stimulation. Similarly, Cersosimo et al. studied MLE in patients with PD and dystonia who underwent pallidal DBS with MER (2). They found that MLE continued in 10 of 11 patients with PD and in 8 of 9 patients with dystonia after 6 months of Globus pallidus internal (Gpi)-DBS. Their study concluded that the presence of MLE after electrode implantation in the Gpi may help predict motor benefit from DBS in patients with PD.

Furthermore, we also observed that MLE had the greatest effect on bradykinesia symptoms. Effects on rigidity were less than those observed for both tremor and bradykinesia. However, these findings were inconsistent with Derrey et al.'s results, which demonstrated improvement rates of 42% (tremor), 37% (rigidity), and 25% (bradykinesia) from baseline (4). Moreover, in Derrey et al.'s study, MLE was assessed on day 3 following DBS of the STN with MER, after at least 12 h of non-dopaminergic treatment, and before pulse generator placement. They found a 27% improvement ratio in the motor score (UPDRS part III) of MLE compared with baseline (off-state) levels.

In the present study, it was hypothesized that MLE is unrelated to the number of microelectrodes because the microelectrodes were placed in the STN at a distance of 2 mm. The approximate STN size is as follows: AP: 5.9 mm, ML: 3.7 mm, and IS: 5 mm (1). Therefore, the motor part of the STN has less volume than the whole and a precise MER-related MLE is not accurately observed in the motor part because the electrodes were located in the limbic or associative parts of the STN. From an electrophysiological perspective, the motor part of the STN is not different from other parts of the STN. Because the limbic and associative side effects related to MLE follow-

ing DBS of the STN were not evaluated in the present study, only the relation between the number of microelectrodes used and MLE was evaluated. STN is a small but crucial junction of the basal ganglia complex that has emotional, cognitive, and motor behavioral functions. Mallet et al. have studied the emotional and motor aspects of behavior following stimulation of STN sub-regions using Atlas/MRI-based localization after DBS of the STN. They observed a hypomanic state when the stimulation was localized to the anteromedial STN; both this contact and the contact immediately dorsal to it improved the parkinsonian motor symptoms. However, the most dorsal and ventral contacts, which are located at the boundaries of the STN, neither induced the behavioral disorder nor improved motor performance. They concluded that the STN is a complex and multifunctional structure, which integrates the motor, cognitive, and emotional components of basal ganglia-controlled behaviors (12).

■ CONCLUSION

MER-induced MLE improved motor symptoms and was not correlated with the number of microelectrodes used during the procedure.

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