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The Impact of Subthalamic Deep Brain Stimulation on Apathy in Parkinson's Disease Patients

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ABSTRACT

AIM: To investigate the impact of subthalamic deep brain stimulation (STN DBS) on apathy and the possible relationship between apathy, depression, and levodopa equivalent dosage (LED) in Parkinson's Disease (PD) patients.

MATERIAL and METHODS: A total of 26 patients have been evaluated via the Unified Parkinson Disease Rating Scale (UPDRS), Beck Depression Inventory (Beck D), and Beck Anxiety Inventory (Beck A), Montreal Cognitive Assessment (MoCA), Parkinson Disease Questionnaire (PDQ-39) just before and 6 months after DBS.

RESULTS: Apathy scores (AES) showed a slight decrease from 54.00 ± 10.30 to 52.69 ± 8.88 without any statistical significance (p=0.502) after DBS therapy. No correlation was detected between the post-treatment changes in apathy and UPDRS scores, Beck D, Beck A. Although the direction of the correlation between changes in AES scores and LED values was negative, the results did not reach statistical significance.

CONCLUSION: STN DBS therapy does not have a negative effect on apathy in PD Patients. Despite the satisfactory motor improvement, conservative dopaminergic dose reduction after surgery seems to be the main point to prevent apathy increase in PD patients after STN DBS.

KEYWORDS: STN-DBS, Parkinson, Apathy

ABBREVIATIONS: AES: Apathy evaluation scale, **Beck A:** Beck anxiety inventory, **Beck D:** Beck Depression inventory, **CAPSIT-PD:** Surgical interventional therapies in parkinson disease, **COMT:** Catechol-o-methyl transferase, **DBS:** Deep brain stimulation, **LED:** Levodopa equivalent dosage, **MAO-B:** Monoamine oxidase-B, **MER:** Intraoperative microelectrode recording, **MoCA:** Montreal cognitive assessment, **PD:** Parkinson's disease, **PDQ-39:** Parkinson disease questionnaire, **STN DBS:** Subthalamic nucleus deep brain stimulation, **SNr:** Substantia nigra pars reticulate, **UPDRS:** Unified parkinson disease rating scale

INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for Parkinson's disease (PD). The main advantage of targeting the STN is related to dopaminergic doses. Dopaminergic medication can be reduced after STN DBS treatment due to significant post-operative motor improvement (6). Apathy is a newly recognized non-motor symptom of PD that has a high impact on quality of life. It is characterized by loss of motivation, lack of initiation, interest, and energy, and flattened affect (22,17). Neuromodulatory treatments like DBS are found to be effective on both motor symptoms and most non-motor features. However, recent studies have demonstrated that apathy may deteriorate after STN DBS treatment in up to 71 % of the patients (7-13,19,26). Post-operative change of apathy

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is controversial and still being debated (4). Neurologists still cannot predict post-treatment outcomes in terms of apathy. The existence of apathy following DBS may have a few underlying mechanisms. The most prominent one is reduced dopaminergic stimulation and mesolimbic denervation following STN DBS (5,23).

We aimed to evaluate apathy in PD patients just before and 6 months after STN DBS. Because optimizing electrode adjustments and antiparkinsonian drug dose titration takes time, we considered 6-month parameters of either motor or non-motor features, including apathy and other cognitive-psychiatric symptoms, along with levodopa equivalent dose (LED) measures.

MATERIAL and METHOD

This is a prospective observational study to determine the impact of STN DBS on apathy. The study protocol was approved by the Ethics Committee of Marmara University, and informed consent was obtained from all participants (Date: 06.01.2017; No: 09.2017.023).

Patient Selection

The study recruited 26 PD patients who were eligible for STN DBS according to the Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD). The Marmara University DBS treatment team consists of expert neurologists and experienced neurosurgeons.

Data Collection

Data was obtained through interviews with patients and caregivers, as well as patient files. The Unified Parkinson's Disease Rating Scale (UPDRS), Apathy Evaluation Scale (AES), Parkinson Disease Questionnaire (PDQ-39), Montreal Cognitive Assessment (MoCA), Beck Anxiety Inventory (Beck A), and Beck's Depression Inventory (Beck D) were applied for patient assessment. Sociodemographic data were also collected, and the levodopa equivalent dose (LED) was calculated for each patient.

Surgery

Intraoperative microelectrode recording (MER) was performed for precise targeting during electrode placement. The movement disorder expert (DIG) performed the intraoperative patient examination and adjusted the stimulus intensity to obtain the best side effect-free clinical response. Fluoroscopy was used to verify the permanent positions of the electrodes. Postoperatively, MRI scans were obtained within 24 hours to verify electrode location and intracerebral hemorrhage control. A cranial CT scan was performed 6 days after the operation.

Clinical Assessment

All preoperative (one week before surgery) and postoperative (6 months) evaluations were performed at medication-on and stimulation-on states. Motor outcomes were assessed using the UPDRS part III, which was also administered under medication-on conditions (both pre- and postoperative). The apathy evaluation scale (AES) was used to evaluate apathy. The AES focuses on the patient's hobbies, occupations in daily life, and enjoyment, and measures loss in these areas. It has 18 items, with a scoring value ranging from 18 to 72, to assess disinterest in behavioral, cognitive, and emotional domains during the last 4 weeks (3). The Turkish validity and reliability study of the scale was performed in 2001 (8).

The PDQ-39, the MoCA, Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI) were used to assess the quality of life and cognitive and psychiatric status. Levodopa equivalent dose (LED) was calculated, including all medications (dopamine agonists, monoamine oxidase B inhibitors, and COMT inhibitors).

Statistical Analysis

R Program version 2.15.3 was used for statistical analysis.

The distribution of the quantitative data was determined using the Kolmogorov-Smirnov test. T-tests and Pearson's correlation analyses were performed for normally distributed variables. Mann-Whitney U tests and Spearman's correlation analyses were performed for non-normally distributed variables.

The p-value for statistical significance was set at <0.05.

RESULTS

26 patients were included in the study.

Demographics

Demographic data of the patients are shown in Table I.

The mean age of onset was 47.03 ± 10.27 (19-62)

The mean disease duration was 13.73 ± 5.39 years (5–25).

The mean age of the patients was 60.38 ± 9.10 (27-72).

The numbers of female and male patients were equal.

Pre and Post-treatment Changes in Scales' Scores and LED

Pre and Post-treatment Changes of Scales' Scores and LED are shown in Table II.

Beck D scores tend to decrease (preoperative 11.31 ± 7.72 to postoperative 9.85 ± 7.26) without significant change (p=0.502).

Table I: Demographic Data of the Patients

Total Patient number (n)	26
Female number	13
Male number	13
Gender (%) (F/M)	50/50
Age (avg ± SD)	60.38 ± 9.10
Age of onset (avg ± SD)	47.03 ± 10.27
Disease duration (avg ± SD)	13.73 ± 5.39

Table II: Comparison of Clinical Scale Scores and Levodopa Doses in Preoperative and Postoperative Periods

	Preoperative	Postoperative 6. month	
Beck A	16.69 ± 9.72	12.00 ± 7.31	**Z=-2.66, p=0.008**
Beck D	11.31 ± 7.72	9.85 ± 7.26	**Z=-0.82, p=0.41**
AES	54.00 ± 10.30	52.69 ± 8.88	df=25, p=0.502
MoCA	18.77 ± 5.12	20.12 ± 4.65	Df=25, p=0.05
UPDRS total	41.08 ± 14.59	25.61 ± 12.94	**Z=-3.94, p<0.001**
UPDRS Part 3	20.04 ± 8.45	11.58 ± 6.69	**Z=-3.88, p<0.001**
PDQ-39	50.46 ± 27.82	35.42 ± 25.41	**Z=-3.01, p=0.003**
LED (mg)	843.26 ± 336.49	672.26 ± 313.98	**Z=-3.001, p=0.003**

AES: *Apathy evaluation scale,* ***Beck A:*** *Beck anxiety inventory,* ***Beck D:*** *Beck Depression inventory,* ***LED:*** *Levodopa equivalent dosage,* ***MoCA:*** *Montreal cognitive assessment,* ***PDQ-39:*** *Parkinson disease questionnaire,* ***UPDRS:*** *Uni ed parkinson disease rating scale.*

Table III: Correlation Between AES, UPDRS, Beck A, Beck D and LED

			AES	UPDRS	Beck A	Beck D	LED
Spearman's rho	**AES**	Correlation coefficient	1.000	-0.014	-0.055	-0.343	-0.173
		Sig. (2-tailed)	.	0.944	0.789	0.086	0.398
		N	26	26	26	26	26
	Beck A	Correlation coefficient	-0.014	1.000	0.186	0.200	-0.096
		Sig. (2-tailed)	0.944	.	0.363	0.328	0.640
		N	26	26	26	26	26
	Beck D	Correlation coefficient	-0.055	0.186	1.000	0.572	-0.173
		Sig. (2-tailed)	0.789	0.363	.	0.002	0.398
		N	26	26	26	26	26
	LED	Correlation coefficient	-0.173	-0.096	-0.173	-0.249	1.000
		Sig. (2-tailed)	0.398	0.640	0.398	0.220	.
		N	26	26	26	26	26

******* *Correlation is significant at the 0.01 level (2-tailed).* ***AES:*** *Apathy evaluation scale,* ***Beck A:*** *Beck anxiety inventory,* ***Beck D:*** *Beck Depression inventory,* ***LED:*** *Levodopa equivalent dosage,* ***UPDRS:*** *Uni ed parkinson disease rating scale.*

MoCA scores (preoperative 18.77 ± 5.12 to postoperative 20.12 ± 4.65) did not change significantly (p=0.05).

Beck A scores decreased (preoperative 16.69 ± 9.72 to postoperative 12.00 ± 7.31) significantly (p=0.008).

PDQ-39 scores improved (preoperative 50.46 ± 27.82 to postoperative 35.42 ± 25.41) significantly (p=0.003).

LED values decreased by around 20% (preoperative 843.26 ± 336.49 to postoperative 672.26 ± 313.98) significantly (p=0.003).

UPDRS total scores decreased (preoperative 41.08 ±14.59 to postoperative 25.61 ± 12.94) significantly (p<0.001).

UPDRS motor scores decreased (preoperative 20.04 ± 8.45 to postoperative 11.58 ± 6.69) significantly (p<0.001).

Apathy scores (AES) showed a slight decrease from 54.00 ± 10.30 to 52.69 ± 8.88 without any statistical significance (p= 0.502).

Postoperative evaluation of the Beck A, LED, UPDRS total score, and PDQ-39 scale revealed significant improvements. The LED decrease was also significant. These results revealed postoperative improvements in motor parameters and quality of life and a reduction in LED values of PD patients.

Comparison of the Scales' Scores

The correlations between AES and UPDRS, Beck A, Beck D and LED are shown in Table III.

This analysis evaluates the correlation between the post-treatment changes in all parameters (AES, MoCA, UPDRS, Beck A, Beck D, LED).

No correlation between changes in AES and UPDRS was detected.

No correlation between changes in AES and Beck A was detected.

No correlation between changes in AES and Beck D was detected.

Although the direction of the correlation between changes in AES scores and LED values was negative, the results did not reach statistical significance.

DISCUSSION

This study was conducted to evaluate the apathy scores of patients after STN DBS treatment and to estimate the correlation between LED and other cognitive/psychiatric features of PD patients. Postoperative apathy was evaluated after the optimization of neurostimulator adjustment and titration of antiparkinson drugs. Cognitive and psychiatric assessments together with motor evaluation were performed just before the surgery and at the 6th month of treatment. The results revealed postoperative improvement in motor parameters and quality of life (PDQ-39). Additionally, LED reduction was detected by around 20%. Apathy scale (AES) scores, on the other hand, slightly decreased after DBS but without statistical significance. No correlation was found between apathy and other variables including LED change, possibly due to the small sample size. However, it is worth noting that a recent meta-analysis did not find a relation between apathy and other neuropsychiatric features, in line with our findings (26).

The impact of STN DBS on apathy is controversial (4,7). EARLYSTIM is the only randomized controlled trial that evaluates apathy after DBS. The best medical treatment and STN DBS groups were assessed in terms of apathy and no difference between the two groups was detected (10). On the other hand, contrary to our results, several other studies revealed a postoperative increase in apathy (7-10,12,13,19,26). These studies mostly explained apathy with the reduced availability of mesolimbic and mesocortical dopamine due to the postoperative dopaminergic drug reduction (4,5,14,18, 23,24). Inconsistent results regarding apathy after DBS may also be due to not only the rapid withdrawal of dopaminergic medications but also the disease progression. The disease duration and the age at the time of the surgery may be contributing factors to postoperative apathy. From this point, the results of the EARLYSTIM trial can be explained by the inclusion of patients who developed early motor complications in the study (15). Since our study was designed to evaluate the correlation between apathy and LED, we do not have data about this hypothesis.

It must be noted that apathy is a complex condition that is often confused with depression and cognitive decline. Although validated apathy scores are available, the mixed nature of apathy can make it difficult for clinicians to recognize and properly diagnose (23). This may contribute to the inconsistent results of studies evaluating post-DBS apathy. However, electrode localization is another contributing factor that has been reported in the literature (20). The STN has three functional areas: motor, associative, and limbic (1,7). In PD patients, the motor portion of the STN is targeted to improve motor function. However, inaccurate placement of the electrode in the associative or limbic areas can potentially lead to non-motor side effects such as apathy. This is supported by a recent case report that showed the alleviation of post-DBS apathy after the electrode was displaced from the limbic site to the motor Area (25). Another study found a significant increase in apathy after STN-DBS. This structural and functional study revealed a correlation between apathy and more dorsolateral stimulation of the STN, only in the left hemisphere. The authors concluded that stimulation of the motor part of the STN itself could induce apathy, rather than inaccurate limbic stimulation (2). Future longitudinal studies that are designed to use alternative contact points could shed further light on this hypothesis.

In our study, we found that LED decreased by around 20% at 6 months after STN DBS treatment. This may be due to the conservative and slow reduction of dopaminergic drugs, which could explain why we found no significant difference between pre- and post-STN DBS apathy scores. The treatment options for patients with post-STN DBS apathy include dopamine agonists with D2 and D3 receptor affinities. Some studies have shown that higher doses of agonists are associated with lower apathy scores, which is likely due to the higher D3 receptor affinity of dopamine agonists. Methylphenidate has also been shown to alleviate fatigue, which is one of the associated symptoms of apathy (24). When Globus Pallidus interna (GPi) was chosen as the target, there was no difference between pre- and post-apathy scores (16). This suggests that less apathy after GPi DBS may be related to less LED attenuation after surgery. However, more comparative studies are needed to confirm this possible correlation. The most important hypothesis for the cause of post-STN DBS apathy is still the hypodopaminergic state caused by the reduction of dopaminergic agents, rather than STN-DBS itself. Another important point to emphasize is that apathy that develops later, independently of electrode location and resistant to dopaminergic therapy, is thought to be a part of the dysexecutive syndrome that occurs as a component of progressive alpha-synucleinopathy (3,18,21).

Our study had several limitations. First, the follow-up period was short, and the small number of patients limited the correlation analysis. Second, electrode placements and stimulation parameters were not included in the analysis. This was because the primary focus of the study was to assess apathy and dose reduction after STN DBS, and the study design did not include data on DBS parameters and electrode placement.

CONCLUSION

Slow LED reduction after STN-DBS is important to prevent post-operative apathy. However, our study did not find a statistically significant correlation between LED reduction and apathy, possibly due to our steady apathy scores. Despite the satisfactory motor improvement, conservative dopaminergic dose reduction after surgery seems to be the main point to prevent apathy increase in PD patients after STN DBS.

Conflicts of interest and Disclosure

The authors declare no conflicts of interest. The study was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent prior to enrollment. This research did not receive any specific grants from public, commercial, or not-for-profit funding agencies. All authors have seen and approved the manuscript in its submitted form. The authors declare that they have conformed to the highest standards of ethical conduct in the submission of accurate data and that they acknowledge the work of others when applicable. The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: DIG, OGO
Data collection: OGO, SJ, AS
Analysis and interpretation of results: OGO, DIG
Draft manuscript preparation: OGO, DIG
Critical revision of the article: DIG
Other (study supervision, fundings, materials, etc...): OGO, DIG
All authors (OGO, SJ, HO, AS, DIG) reviewed the results and approved the final version of the manuscript.

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