APATHY & COGNITIVE SYMTOMS IN DEEP BRAIN STIMULATION

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Abstract

Objective: The aim of this research was to elucidate the effect of deep brain stimulation on apathy, and cognitive functions in the pre and post-operative period. Materials & Methods: This study was conducted in Adana City Training & Research Hospital, Parkinson and Movement Disorders Center between January to December 2022. Individuals were evaluated by a multidisciplinary commission consisting of neurology, neurosurgery and psychiatrists. Thirty six, aged between 18–70 years who underwent Deep Brain Stimulation at the neurosurgery clinic were included in the study. Hamiltonanxiety and depression, apathy assessment, standard mini-mental test and Montreal Cognitive Assessment scales are applied to the patients. Results: The mean Apathy Score at the pre-op was 47.77±15.83 in patients who had undergone DBS operation while it was 30.83±13.59 in the post–op. This decrease was statistically significant ($p<0.003$) and indicated clinical improvement. The average Hamilton Anxiety scale scores at the pre–op was 11.50±5.14, and s 10.22±5.57 at the post-op with no clinical significance ($p=0.28$). The UPDRS-ON value was determined as 22.55±7.53 in the pre–op and 14.50±6.99 in the post–op significantly ($p<0.001$). UPDRS-OFF was found to be significant with pre–op 37.44±9.85, compared to post–op 23.44±7.86 ($p<0.001$). Conclusion: Regarding the results of this study, it was found that sub – thalamic stimulation led to stabilization of both motor and non-motor complications. Additionally DBS ameliorated apathy and Parkinson's Disease symptoms of patients significantly. Future studies with larger sample size that focus on both pharmacological and non-pharmacological treatments might provide better clinical aspects.

ORIGINAL RESEARCH ARTICLE

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COMPARISON of APATHY & COGNITIVE SYMPTOMS IN PRE- AND POST-OPERATIVE PERIOD IN DEEP BRAIN STIMULATION SURGERY

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ABSTRACT

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Materials & Methods: This study was conducted in Adana City Training & Research Hospital, Parkinson and Movement Disorders Center between *January to December 2022* . Individuals were evaluated by a multidisciplinary commission consisting of neurology, neurosurgery and psychiatrists.Thirty six,aged between 18 – 70 years who underwent Deep Brain Stimulation at the neurosurgery clinic were included in the study. Hamiltonanxiety and depression, apathy assessment, standard mini-mental test and Montreal Cognitive Assessment scales are applied to the patients.

Results: The mean Apathy Score at the pre-op was 47.77±15.83 in patients who had undergone DBS operation while it was 30.83±13.59 in the post –op. This decrease was statistically significant *($p<0.003$)* and indicated clinical improvement. The average Hamilton Anxiety scale scores at the pre – op was 11.50±5.14, and s 10.22±5.57 at the post – op with no clinical significance *($p=0.28$)* . The UPDRS-ON value was determined as 22.55±7.53 in the pre –op and 14.50±6.99 in the post –op significantly *($p<0.001$)* . UPDRS-OFF was found to be significant with pre –op 37.44±9.85, compared to post –op 23.44±7.86 *($p<0.001$)* .

Conclusion: Regarding the results of this study, it was found that sub – thalamic stimulation led to stabilization of both motor and non-motor complications. Additionally DBS ameliorated apathy and Parkinson's Disease symptoms of patients significantly. Future studies with larger sample size that focus on both pharmacological and non-pharmacological treatments might provide better clinical aspects.

Keywords: *Parkinson's disease, psychiatric symptoms, apathy, cognitive functions, deep brain stimulation*

DERİN BEYİN STİMULASYONU UYGULANAN HASTALARDA AMELİYAT ÖNCESİ VE SONRASI APATİ VE KOGNİTİF BELİRTİLERİN KARŞILAŞTIRILMASI

ÖZET

Dayanak: Parkinson hastalığında psikiyatrik belirtiler dopamin, serotonin, nor-adrenalin ve asetilkolin gibi nörotransmiterlerin kaotik etkileşimi ve değişimi sonucu ortaya çıkar.

Amaç: Bu araştırmanın amacı, derin beyin stimülasyonunun ameliyat öncesi ve sonrası dönemde apati ve bilişsel işlevler üzerindeki etkisini ortaya koymaktır.

Gereçler ve Yöntem: Bu araştırmaya, Adana Şehir Eğitim ve Araştırma Hastanesi Parkinson ve Hareket Bozuklukları Merkezine başvuran yaşları 18 – 70 yaş arasında nöroloji, beyin ve sinir cerrahisi ve psikiyatri hekimlerinden oluşan bir komisyon tarafından multidisipliner bir çalışmayla değerlendirilen, *2022 Ocak – 2022 Aralık* ayları arasında beyin cerrahi kliniğince Derin Beyin Stimülasyonu uygulanan 36 hasta dahil edilmiştir. Hastalara Hamilton anksiyete ve depresyon ölçeği, apati değerlendirme ölçeği, standart mini mental test ve Montreal Bilissel Degerlendirme ölçeği uygulanmış operasyon öncesi ve sonrası ölçek değerleri karşılaştırılarak değerlendirme yapılmıştır.

Bulgular: DBS operasyonu geçiren hastalarda ameliyat öncesi 0. ayda ortalama Apati Skoru 47.77±15.83 iken ameliyat sonrası 6. ayda 30.83±13.59 idi. Bu azalma istatistiksel olarak anlamlıydı *($p<0.003$)* ve klinik

iyileşmeyi gösterdi. Ameliyat öncesi 0. ayda ortalama Hamilton Anksiyete ölçeği puanları 11.50±5.14, ameliyat sonrası 6. ayda s 10.22±5.57 idi ve klinik anlamlılık yoktu*(p=0,28)* . UPDRS ON değeri ameliyat öncesi 0. ayda 22.55±7.53, ameliyat sonrası 6. ayda anlamlı olarak 14.50±6.99 olarak belirlendi*(p<0.001)* . UPDRS OFF ameliyat öncesi 0. ay 37.44±9.85 ile ameliyat sonrası 6. ay 23.44±7.86 ile anlamlı bulundu

(p<0.001).

Sonuç: Bu çalışmanın sonuçlarına bakıldığında, sub-talamik stimülasyonun hem motor hem de motor olmayan komplikasyonların stabilizasyonuna yol açtığı bulundu. Ek olarak, DBS hastaların apati ve Parkinson Hastalığı semptomlarını önemli ölçüde iyileştirmiştir. Hem farmakolojik hem de farmakolojik olmayan tedavilere odaklanan daha büyük örneklemli gelecekteki çalışmalar daha iyi klinik yönler sağlayabilir.

Anahtar kelimeler: *Parkinson hastalığı, psikiyatrik belirtiler, apati, kognitif fonksiyonlar, derin beyin stimülasyonu*

Abbreviations:

AAS : Apathy assessment scale

DBS : Deep Brain Stimulation

GPi : globus pallidus internus

HAM – A : Hamilton anxiety scale

HAM – D : Hamilton depression scale

IPD : Idiopathic Parkinson's disease

MMSE : mini mental state examination

MoCA : Montreal Cognitive Assessment Scale

NICE : National Institute of Clinical Excellence

NMS : non-motor symptoms

PD : Parkinson's Disease

SD : Standard Deviation

SMMT : standard mini-mental test

SPSS : Statistical Package for the Social Sciences

STN : sub-thalamic nucleus

UPDRS : Unified Parkinson's disease rating scale

Introduction

Idiopathic Parkinson's disease *(IPD)* is the second most common neurodegenerative disease after Alzheimer's disease and affects approximately 1.8% of the population over 60 years of age *(1)* . The main clinical symptoms are resting tremor, bradykinesia, rigidity and postural reflex disorder. Although it is considered a movement disorder and recognized by cardinal motor signs and symptoms, these are just the tip of the iceberg *(2, 3)* .

Parkinson's disease is classified as a neuropsychiatric disorder because of the non-motor symptoms *(NMS)* including cognitive, mood, autonomic and sleep disorders, as well as the motor symptoms that complicate the patients' lives, both in the pre-motor stage and throughout the entire course of the disease as it directly affects the quality of life and independence of the person *(4)*. Regarding this fact, the analogy of the perfect storm, which means a situation in which many bad things happen at the same time, consists of a combination of motor and non-motor symptoms.

Non-motor symptoms have common etiopathogenesis with the motor symptoms of Parkinson's disease, and emerge as adverse effecys of thetreatment in Parkinson's disease. It has been suggested that psychiatric symptoms arise as a result of the chaotic interaction and change of neurotransmitters such as dopamine, serotonin, nor-adrenaline and acetylcholine, beyond trying to understand the basis of a single one *(5).* In previous literature it was reported that certain psychiatric diseases such as depression anxiety disorder schizophrenia are risk factors for Parkinson's disease. In this context, Parkinson's disease is a very complex and chronic disease *(6)* .

Parkinson's disease treatment can be divided into two as medical and surgical. In order to achieve a better levodopa response in Parkinson's disease, surgical treatment as deep brain stimulation treatment of subthalamic nucleus *(STN)* and globus pallidus internus *(GPi)* is applied *(Evidence Level – 1)* . According to UK National Institute of Clinical Excellence *(NICE)* guidelines, individuals must be resistant to medical therapy, have side effects depending on the medication, and be medically and psychologically fit with prolonged 'off' periods *(7).*

Deep Brain Stimulation *(DBS)* is the most commonly used surgical method for the motor symptoms of Parkinson's disease. In this procedure, microelectrodes are placed in one of the two regions of the brain *(subthalamic nucleus or globus pallidus region)* in order to give high-frequency electrical stimulation *(8)* . This stimulation regulates the signal that is missing in Parkinson's patients. DBS surgery is the most preferred surgery as it is safe, effective, fully reversible and adaptable to the patient. This treatment is applied to patients who are resistant to drugs or have side effects *(9)* .

In this research, we aimed to elucidate the effect of deep brain stimulation on apathy and cognitive functions in the pre and post-operative period. We believe that the outcomes of this study will to improve the clinical applications and provide better clinical usage.

Materials & Method

A total of 36 patients aged between 18 – 70 years, who were diagnosed with Parkinson's disease and followed up in the neurology clinic of our institution have been enrolled within the scope of this research. The patients were evaluated by a commission of specialists consisting of neurologist, neurosurgeon, and psychiatrist in a multidisciplinary approach. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation *(institutional and national)* and with the Helsinki Declaration of 1975, as revised in 2008. Ethics committee approval has been granted from our institution at *10/05/2022* with protocol number *1928* and informed consent has been obtained from all participants.

Inclusion Criteria

Patients aged between 18 – 70 years, who were diagnosed with Parkinson's disease, followed-up in the neurology clinic of our institution, and who underwent DBS in neurosurgery between *28/01/2022 and 31/12/2022* were included in the study. Individuals were required to be literate, volunteered to participate in the study and had no psychiatric history *(affective disorder, severe anxiety, psychotic history, suicidal history, major depression, manic episodes, bipolar affective disorder, without personality disorders).*Each patient was evaluated by a psychiatrist and psychologist for their apathy level before and after DBS.

Exclusion Criteria

Patients with severe disease symptoms or hearing/speech disabilities preventing them to cooperate during clinical or laboratory evaluations, serious or uncontrolled medical conditions *(hepatic, renal, gastroenterological, respiratory, cardiovascular, neurological, or oncological)* were excluded.

Sociodemographic Data Form, Structured Clinical Interview – Clinician Version for DSM-5 Disorders, Ham – A and Ham – D scales, Yale Brown Obsession Compulsion Sscale, Barret Impulsivity Scale, Apathy Assessment Scale, Arizona Sexual Experience Scale, MoCA and standard mini mental test were applied to each patient.

The procedure was conducted under local anesthesia. Special and permanent electrodes were placed to the target points of the brain. In the last part of the surgery, a high-tech battery was placed under the skin in the chest area and connected to the electrodes placed in the brain. The total processing time was on average 5 – 6 hours.

Statistical Analysis

The analysis of data has been conducted via Statistical Package for the Social Sciences 25.0 *(SPSS)* . *Descriptive statistics* have been given as *mean ± standard deviation or median-quartile* width according to the distribution of continuous variables. *Categorical variables* were summarized as *numbers and percentages* . In the main group, the participants were divided as those with pre-operative diagnosis and those without. The cut off value in the applied scales, have been interpreted those above and those without. *Normal distribution* parameters have been analyzed via *t – test* for the comparison between groups. The *normality* has been examined by*Shapiro Wilks test.* If the distribution was not normal, the comparison of two *independent groups* has been performed with*Man Whitney U test. Dependent* variables were ordinal and continuous. *Chi-square test* has been utilized in the analysis of*categorical variables.* A p value of *0.05* has been considered as statistically significant.

Results

Distributions of baseline demographic, age of onset of Parkinson's disease and duration of disease were denoted in *Table 1* . The mean age of the individuals was 55.22±8.68 years. Gender distirbution was as follows: 44.4% *(n=16)* were female and 55.6% *(n=20)* were male. When the marital status was investigated, 100% of the 36 patients were married. Only 22.2% of the patients had a job. The mean age at onset of Parkinson's disease was 40.39±13.78 years, and the duration of the disease was 14.72±9.39 years. Comorbid diseases was; diabetes in 8*(22.2%)* and hypertension in 8*(22.2%)* patients.

Twenty subjects *(55.6%)* had Parkinson's disease and 4 patients*(11.1%)* had a history of psychiatric illness in their family. Ten individuals *(27.8%)* used psychiatric medication and 18 patients *(50%)* had depressive symptoms *(Table 2)* .

While the mean value of Apathy Score at the pre – operative 0^{th} month was 47.77±15.83 in patients who had undergone DBS operation, it was 30.83±13.59 in the post – operative 6^{th} month. This decrease was statistically significant*($p<0.003$)* and indicated clinical improvement. The average of Hamilton Anxiety scale scores at the pre – operative 0^{th} month was 11.50±5.14, and determined as 10.22±5.57 at the post – operative 6^{th} month with no clinical significance *($p=0.28$)* . The UPDRS ON value was determined as 22.55±7.53 in the pre – operative 0^{th} month and 14.50±6.99 in the post – operative 6^{th} month significantly *($p<0.001$)* . UPDRS OFF was found to be significant with pre – operative 0^{th} month 37.44±9.85, compared to post – operative 6 month 23.44±7.86*($p<0.001$)* .

The effective dose of levadopa was 1416.38±341.72 mg in pre operative 0^{th} month and 977.77±317.60 post – operative 6^{th} month *(Table 3)* .

Discussion

In this study, the effect of bilateral sub-thalamic nucleus deep brain stimulation on apathy was investigated. The mean age of Parkinson's disease patients who underwent STN DBS in the literature varied between 50.4±9.8 to 63.4±6.4 years, and the duration of the disease was between 7.5±2.9 to 18.8 ±6.1 years *(10 – 12)*. In our study, the mean age was 55.22±8.68 years and duration of disease was 14.72±9.39 years.

Advanced age is considered a relative contraindication for DBS and 70 years old is considered as an advanced age in many centers as it is often associated with faster progression of PD leading to rapid decline in cognitive functions, increased burden of comorbidity and greater brain atrophy. A minimum duration of 4 years of motor symptoms is recommended to confidently accept the diagnosis and documenting a good levodopa response may not be possible earlier than this. DBS in PD is typically performed within 11 – 13 years of illness, with progression of the disease leading to an increase in motor complications and a decrease in

quality of life. Recent studies denoted that DBS outperforms the best medical treatment in younger group of patients with lower surgical risk *(13).*

In previous literature it was reported that sub-thalamic nucleus deep brain stimulation improved motor fluctuations, dyskinesia, and quality of life in advanced Parkinson's disease *(14, 15)* . However, its effects on the processes underlying mood and behavior disorders are complex and certainly multifactorial. Therefore, the published articles presented contradictory outcomes *(16)* . *Drapier et al. (2006)* enrolled 15 patients who underwent STN DBS in the pre – operative period and 3^{rd} and 6^{th}months post – operatively and found a deteriorated apathy scores and although there was a therapeutic improvement in motor symptoms. Regarding this STC DBS may directly contribute to the development of apathy by affecting the limbic system *(17)* .

The *EARLYSTIM* study, in which patients were treated with bilateral sub-thalamic stimulation plus medical therapy, evaluated behavioral outcomes in a relatively large group of patients. Less neuropsychiatric fluctuations were observed in those receiving STN DBS plus medical treatment. Although dopaminergic replacement has been reduced in the early period despite the risk of developing acute withdrawal *(including apathy, depression, and anxiety in the following years)* , both motor and non – motor symptoms were stabilized at a higher rate compared to the group that received only medical treatment. Additionally, antidepressant and antipsychotic requirements of the patients were reduced. In the same study, they stated that the frequency of apathy was not different in both patient groups, but they achieved higher apathy scores in patients who received subthalamic stimulation *(18)* . Similar to their findings the levodopa dose has also been reduced significantly in our study.

All previously published literature seems to agree that dopamine agonist treatment achieves a rapid reduction of apathy scores. In our study, a significant decrease was observed in apathy scores at the 6^{th} month after the operation. We think that the gradual reduction of dopaminergic treatments is extremely important, and the accompanying medical treatment should be optimized for STN DBS in order to ameliorate apathy scores. Reduction of dopaminergic drugs in parallel with increased sub-thalamic stimulation after surgery and cautious re – introduction of dopaminergic drugs in case of withdrawal apathy enables a better recovery while maintaining motivation and quality of life *(19, 20)* .

Another issue to be considered can be elaborated as the decrease in apathy after the initiation of dopaminergic treatment in early-stage Parkinson's disease *(but this decrease does not last permanently)* . On the contrary, apathy increases to 40% in patients without dementia and 60% in patients with dementia 5 – 10 years after the onset of disease *(21 – 24).* Considering the behavioral complications of dopaminergic treatments such as impulse control disorders, hallucinations, or delirium, it is obvious that the target in treatment is not only the correction of motor symptoms. In our study, while the pre – operative levodopa equivalent dose was 1416.38±341.72 mg, it decreased to 977.77±317.60 mg in the 6^{th} month of the post – operative period and this decrease was found to be statistically significant. According to the outcomes of this study, while the BPHDS *(I – III)* Off period values w significantly decreased in the post – operative period *($p<0.001$)* . These figures indicated that the patients had the opportunity to reduce the dopaminergic treatment dose by up to 70%, and to improve their motor symptoms by 60%.

Similar to our study, it was previously shown that STS DBS improved motor scores by 50% on average *(25)* . Although anhedonia overlaps to a large extent with an emotional expression of apathy *(26),*studies have shown that isolated apathy is a disorder not associated with cognitive impairment or depression in the early and advanced stages of Parkinson's disease *(27, 28)* . Approximately half of the patients with apathy do not have accompanying depression or cognitive impairment. Therefore, apathy in PD patients can be considered as a separate clinical entity *(29, 30).*

There is a strong relationship between parkinsonism and depression. Published articles indicated that depression is diagnosed in Parkinson's patients 2 times more often than the general population, and accompanying depressive symptoms are motor – related. Depression exerts a very important effect in terms of affecting the quality of life by aggravating the symptoms even more *(31 – 33)* . Depression rates varied between 30% and 50% according to the methodological differences and was found to be 44% in our study. At this stage

one should ask whether the accompanying depression developed as a reactive response to the current illness and psychosocial difficulties or is it due to neuro – degeneration. In our study, Hamilton depression scores decreased significantly at the post – operative period *(p=0.025)* .

Cognitive disorders are rarely diagnosed in Parkinson's disease. Even in the early stages, cognitive impairment increases and even progresses to dementia in the following years. Results from many studies have shown that executive dysfunction was correlated with apathy *(34, 35)* . In our study, the change in the mean of minimental test *(MMSE)*and Moca values in the pre – operative and post – operative period was not significant, and relatively high pre – operative scores affected the scores of post – operative cognitive impairment.

The presence of apathy is predictive of more severe motor symptoms, worsened cognitive status, poor quality of life, greater caregiver burden, and decreased functionality. The inability of the person to perform the activities of daily living, the decrease in the treatment response, means that the individual becomes dependent on someone else for the continuation of life *(36)* . A comprehensive and multidisciplinary approach based on the bio – psychosocial model for the recognition, assessment, and management of each psychiatric symptoms on the invisible parts of the iceberg makes an important contribution to calming the storm and tailoring interventions to the needs of each patient in Parkinson's disease *(37)* .

Conclusion

Regarding the results of this study, it was found that sub – thalamic stimulation led to stabilization of both motor and non-motor complications. Additionally DBS ameliorated apathy and depression symptoms of the patients significantly. Future studies with larger sample size that focus on both pharmacological and non-pharmacological treatments might provide better clinical aspects.

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Competing interests

The authors declare that they have no competing interests.

Ethical Declaration

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