Turk Neurosurg 30(1):43-47, 2020

Original Investigation

DOI: 10.5137/1019-5149.JTN.25028-18.3

Received: 05.10.2018
Accepted: 27.04.2019
Published Online: 03.06.2019

Predictive Factors for Favorable Outcome from Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

Seyda ERDOGAN[1], Ali SAVAS[2], Nursel AYDIN[1], Muhittin Cenk AKBOSTANCI[1]

[1]Ankara University, Faculty of Medicine, Department of Neurology, Ankara, Turkey
[2]Ankara University, Faculty of Medicine, Department of Neurosurgery, Ankara, Turkey

This study has been presented at the 18th International Congress of Parkinson's Disease and Movement Disorders between 8 and 12 June 2014 at Stockholm, Sweden.

Corresponding author: Seyda ERDOGAN ✉ dr_seyda@yahoo.com

ABSTRACT

AIM: To investigate predictive factors for a favorable outcome from subthalamic nucleus-deep brain stimulation (STN-DBS) in Parkinson's disease (PD) and whether low serum vitamin B12 (vB12) levels can predict an unfavorable outcome.

MATERIAL and METHODS: Thirty-nine patients with PD who underwent bilateral STN-DBS were retrospectively analyzed. A difference of at least 30% between preoperative medication-off and postoperative medication-off stimulation-on Unified PD Rating Scale (UPDRS)-III scores was accepted to be a good outcome. Patients with good and bad outcomes were compared in terms of age, gender, levodopa responsiveness, vB12 levels, UPDRS subscores, presence of diabetes mellitus and hypertension, and presence of lacunes on cranial magnetic resonance imaging (MRI).

RESULTS: Twenty-two of 39 patients (56.4%) had a good outcome postoperatively. No significant difference was observed in terms of age, gender, presence of abnormal MRI findings, and comorbid diseases between patients with good and bad outcomes. Mean preoperative bradykinesia score in patients with a good outcome was higher than those with a bad outcome. There was a positive correlation between the benefit of STN-DBS and preoperative levodopa responsiveness. In patients with low vB12 levels, 33.3% had a good outcome, whereas 55.2% of patients with normal vB12 levels had a good outcome ($p = 0.589$).

CONCLUSION: Our results confirm that patients with better levodopa response have better outcomes. Interestingly, patients with worse bradykinesia had a better surgical outcome. A favorable surgical outcome was less frequent in patients with low vB12 levels and was not statistically significant.

KEYWORDS: Parkinson's disease, Subthalamic nucleus, Deep brain stimulation, Outcome, Predictive factors, Vitamin B12

INTRODUCTION

Most symptoms of Parkinson's disease (PD) are well controlled by dopaminergic drugs. However, long-term medical treatment is associated with motor fluctuations and levodopa-induced dyskinesias. The duration of "off periods" increases over time and levodopa-induced dyskinesias become difficult to manage. Therefore, the therapeutic window narrows over years. Subthalamic nucleus-deep brain stimulation (STN-DBS) has been an adjunctive therapy for motor fluctuations and levodopa-induced dyskinesias in patients with PD. As revealed by several controlled studies, STN-DBS is associated with approximately 50% decrease in fluctuations, dyskinesias, and drug doses (6,14). The factors associated with a favorable outcome from STN-DBS are good levodopa response, young age (<65), absence of cognitive and psychiatric disorders, and normal cranial magnetic resonance imaging (MRI) findings (16, 23). Despite careful selection, every patient does not respond well to this treatment. In a study with patients complaining of suboptimal response to DBS, the most frequent reasons determined for treatment

Seyda ERDOGAN : 0000-0002-4113-2080 Ali SAVAS : 0000-0002-4150-0795 Nursel AYDIN : 0000-0003-1502-370X
Muhittin Cenk AKBOSTANCI : 0000-0001-5808-5121

failure were poor patient selection, electrode misplacement, and inadequate programming (12).Vitamin B12 (vB12) is an essential vitamin for the nervous system. Neuropsychiatric conditions, such as subacute combined degeneration, polyneuropathy, optic atrophy, and cognitive and mood disorders, associated with vB12 deficiency have been described (3). In our clinical experience, response to STN-DBS may be better in patients who have normal serum vB12 levels than in those patients with low serum vB12 levels.This study aims to assess predictive factors for a favorable outcome from STN-DBS in patients with PD and to investigate whether low serum vB12 levels can predict an unfavorable outcome.

MATERIAL and METHODS

Thirty-nine patients with PD who underwent bilateral STN-DBS between 2005 and 2012 were retrospectively analyzed. Preoperative vB12 levels were analyzed 1 week before STN-DBS. Pre- and postoperative Unified PD Rating Scale (UPDRS) scores were calculated 1 and 1–4 weeks (mean: 1.5 weeks) before and after STN-DBS, respectively.

A difference of at least 30% (improvement) between preoperative medication-off and postoperative medication-off stimulation-on UPDRS-III scores, which evaluates motor symptoms, was accepted to be a good outcome (18). Patients with good and bad outcomes were compared in terms of age; gender; levodopa responsiveness; preoperative vB12 levels; UPDRS subscores of bradykinesia, rigidity, tremor, postural instability, dyskinesias, and wearing off; presence of diabetes mellitus (DM) and essential hypertension (HT); and presence of lacunes on cranial MRI. The correlation between the values [(preoperative medication-off UPDRS-III score minus postoperative medication-off stimulation-on UPDRS-III score) and (preoperative medication-off UPDRS-III score minus preoperative medication-on UPDRS-III score)] were also studied to evaluate the effects of levodopa responsiveness.

The Mann–Whitney *U* and Wilcoxon tests were used to compare continuous variables, whereas the chi-square and Fisher's exact tests were used to compare categorical variables between groups. Correlation between two continuous variables was assessed using Spearman's correlation coefficient. Analyses were performed using IBM SPSS Statistics for Windows version 20. A p-value<0.05 was considered as statistically significant.

RESULTS

A total of 39 patients [19 females; 20 males; mean age: 56.21 ± 8.6 (range: 30–69) years] were included in the study. The mean disease duration was 11 ± 5.7 (range: 3–25) years.

There was a significant difference between preoperative medication-off and postoperative medication-off UPDRS total scores (Table I). When the pre- and postoperative medication-off UPDRS scores were compared, 33.13% improvement in UPDRS-III scores (motor symptoms), 60.33% improvement in UPDRS-dyskinesia scores (items 32, 33, 34, and 35 of UPDRS), and 42.22% improvement in UPDRS-motor fluctuation scores (items 36, 37, 38, and 39 of UPDRS) were detected (Table II). Nineteen of 39 patients (49%) had a dyskinesia score of 0 postoperatively, whereas their score was >1 preoperatively. Twenty-two (10 males; 12 females) of 39 patients (56.4%) had a good outcome, with at least a 30% decrease (improvement) in medication-off UPDRS-III scores. However, 17 (10 males; 7 females) of 39 patients (43.6%) had a bad outcome. The mean ages were 59.3 ± 4.5 and 53.8 ± 10.3 in the bad-outcome and good-outcome groups, respectively (p=0.8). When patients older than and younger than 60 years (17 and 22 patients, respectively) were compared, 15 of the younger patients (68.2%) had a mean disease duration of 11.3 ± 6.7 (bad-outcome group), whereas 7 (31.8%) had a mean disease duration of 11.2 ± 5 (good-outcome group) (p=0.78). No statistically significant difference was found between the scores of the patients with good and bad outcomes in terms of age, sex, disease duration, preoperative rigidity, tremor, and postural instability. Patients with greater than five lacunar lesions on cranial MRI were compared with those who had less than five lesions. Only six patients had greater than five lacunar lesions on cranial MRI. Four of them (66.7%) had a bad response, whereas the other two (33.3%) had a good response. In the patients with less than five lacunar lesions, 60.7% had a good response; however, the difference was not statistically significant (p=0.2). No correlation was observed between the success of surgical treatment and the presence of abnormal MRI findings, comorbid diseases, and vB12 deficiency.

The mean preoperative bradykinesia score was higher (worse) in patients with a good outcome than in patients with a bad outcome (11.52 and 8.41, respectively; p=0.004). There was a positive correlation between the benefit of STN-DBS (preoperative medication-off UPDRS-III score minus postoperative medication-off stimulation-on UPDRS-III score) and preoperative levodopa responsiveness (correlation coefficient = 0.475; p=0.003).

Serum vB12 levels of <126.5 pg/ml was defined as vB12 deficiency. In patients with low levels of vB12, 33.3% had a good outcome, whereas 55.2% of patients with normal vB12 levels had a good outcome. The difference was not significant (p=0.589) (Figure 1).

DISCUSSION

Clinical Outcome After STN-DBS in Patients with PD

Previous studies have reported that STN-DBS provides 28%–60% improvement in UPDRS-III scores (1,2,13,18) and 59%–78% improvement in dyskinesia scores (4,6,17). Similar to previous reports, we found 33.13% improvement in UPDRS-III scores, 60.33% improvement in dyskinesia scores, and 42.22% improvement in motor fluctuation scores.

Age

It has been reported that being young may be a predictor of good outcome (14). Some studies have shown that being old was a predictor for cognitive impairment after STN-DBS (16,20). In a randomized controlled trial, similar improvement was obtained in patients older than and younger than 70 years.

Table I: The Pre- and Postoperative UPDRS Total Scores

	Preop medication off (preop off)	Postop medication off (postop off)	p
Mean ± SD	66.87 ± 18.10	38.30 ± 16.65	**<0.001**
Median (min-max)	64 (36-117)	36 (10-73)	

SD: *Standard deviation,* ***min:*** *Minimum,* ***max:*** *Maximum,* ***UPDRS:*** *Unified Parkinson's Disease Rating Scale.*

Table II: Clinical Outcome Features After Subthalamic Deep Brain Stimulation

	Improvement (%)		
	Mean	**Median**	**Standard Deviation**
UPDRS-III	33.13	38.88	28.70
Dyskinesia	60.33	100.0	122.07
Motor fluctuations	42.22	50.0	43.88

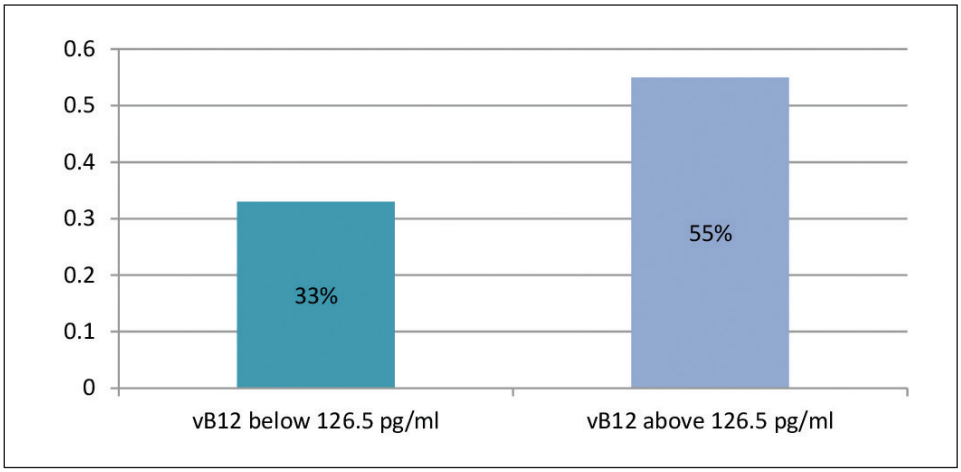

Figure 1: Percentage of patients with a good clinical outcome in terms of vitamin B12 levels.

However, adverse events, such as intracranial hemorrhage, were more common in the elderly (22). In general, old age can be a relative risk factor. In our study, all patients were <70 years of age. When patients older and younger than 60 years were compared in terms of response to STN-DBS, there was no significant difference. We did not observe any adverse events in our study.

Disease Duration

Some studies have reported that a short disease duration may be a predictor of good outcome (14,21). In a study focused on the predictive factors for a good outcome from STN-DBS in patients with PD, no effect of disease duration was observed (23). Since multisystem atrophy may have levodopa response for 5 years, STN-DBS should not be considered before 5 years in patients with PD (19). The disease durations were 11.23 ± 4.94 years in patients with a good outcome and 11.31 ± 6.75 years in those with a bad outcome. The difference was not significant.

Findings on Cranial MRI

Patients with findings suggestive of small-vessel disease or cortical atrophy on cranial MRI may not be good candidates for surgical treatment of PD (9). In our study, 33.3% of patients who had greater than five lacunes on cranial MRI and 60.7% of those who had less than five lacunes had a good response. The difference was not significant, but this may have been due to the small sample size used.

Comorbid Systemic Diseases

The presence of common systemic diseases, including HT, DM, and hyperlipidemia (HL), were evaluated in the elderly. Among the patients, 51.3% had HT. In total, 45% of patients with HT and 68.4% of those without HT showed a good response to STN-DBS; the difference was not significant. HL and DM were observed in only 3% of patients. Therefore, statistical analyses were not performed for these parameters. Literature suggests that HT should be aggressively treated because of the risk of intracranial hemorrhage during the perioperative period (16).

Preoperative Motor Symptoms

Previous studies have reported postural instability, which may not respond well to levodopa, to be a negative predictor of STN-DBS outcome (6,23). Our study showed that there was no difference between patients with good and bad outcomes in terms of preoperative medication-off rigidity, tremor, and postural instability scores. However, preoperative bradykinesia scores were higher in patients with a good outcome than in the patients with a bad outcome (11.52 ± 3.31 and 8.41 ± 2.74, respectively; p=0.004). Based on this result, good responses may be obtained in patients with high preoperative bradykinesia scores with STN-DBS.

Levodopa Responsiveness

Good levodopa response is a well-known predictor of good outcome in STN-DBS (5,11,23). Consistent with these previous results, a correlation between preoperative levodopa responsiveness and good clinical outcome was observed.

Serum vB12 levels: In a study that compares cerebrospinal fluid vB12 and homocysteine levels in patients with PD and normal subjects, vB12 levels were lower in patients with PD, whereas homocysteine levels were higher in patients with PD (15). In this situation, the cause-and-effect relationship is not clear. High homocysteine levels may play a role in the pathogenesis of neurodegenerative disorders (8). On the other hand, some authors have reported that levodopa treatment may cause acquired hyperhomocysteinemia (7,10). Based on our clinical experience, we believe that there may be a correlation between vB12 levels and clinical outcomes after STN-DBS. To the best of our knowledge, this is the first study that investigates the effect of vB12 levels on the response to STN-DBS in patients with PD. In our study, patients with low vB12 levels showed less improvement after STN-DBS (33% vs. 55%), but the difference was not statistically significant.

CONCLUSION

As uniformly reported, good levodopa response is associated with a favorable outcome in the present series. An interesting finding is that the patients with worse bradykinesia may have a better surgical outcome. However, a favorable surgical outcome is much less frequent in patients with low vB12 levels, but this difference is not statistically significant. Further studies with a larger number of participants may clarify this issue.

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