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Risk Factors for Psychiatric Complications after Deep Brain Stimulation in Patients with Parkinson's Disease: An Observational Study

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Abstract

Background: Deep brain stimulation (DBS) of the subthalamic nucleus is an effective treatment option for patients with Parkinson's disease (PD). The risk factors associated with the occurrence of psychiatric symptoms have not been completely elucidated.

Methods: We conducted a naturalistic observational study on patients with PD who would be subjected to DBS. Clinical data, including motor functions, cognitive functions, mental status, and daily dosage of anti-PD drugs were monitored. A psychiatrist evaluated their psychiatric symptoms at the initial assessment, three months, and one year after DBS.

Results: We evaluated 44 participants with PD, of which 32 were subjected to DBS. Thirteen participants were diagnosed with mental disorders at the initial assessment. Twenty-six patients were reassessed at three months after surgery, and 19 participants were reassessed at one year. At three months, the motor function of the participants was significantly improved, and the mean anti-PD drug dose was significantly decreased. Sixteen participants were experiencing some psychiatric symptoms, of which 12 were considered as worsened due to DBS, whereas 6 participants experienced improved mental state. At one year, 6 participants were suffering from some psychiatric symptoms caused by DBS, whereas improvement was observed in 6 participants. An exploratory analysis revealed that participants without dopamine dysregulation syndrome (DDS) at the screening were likely to improve their psychiatric symptoms.

Conclusion: Although DBS caused some psychiatric complications, mental status was improved in some patients in a longitudinal course. DDS is possible to predict poor outcome in psychiatric complication after DBS in PD patients.

Keywords: Parkinson's disease; Deep brain stimulation; Subthalamic nucleus; Psychiatric complication; Risk factor

Introduction

Parkinson's disease (PD) is a progressive age-associated neurodegenerative disorder, which causes motor disability [1], with a prevalence rate of 0.3% in the general population [2]. Tremor, rigidity, akinesia, and postural instability are common symptoms observed in PD, whereas non-motor symptoms such as constipation and orthostatic hypotension can also occur. Other comorbidities include psychiatric symptoms such as anxiety, depression, and hallucination [3]. Some patients with PD present with problematic behaviors based on their impulsiveness [4]. Oral dopamine agonists are commonly prescribed for PD, as dopaminergic neuronal degeneration of the substantia nigra is known to cause movement disorders in PD. Levodopa, dopamine agonists, and other drugs with dopamine-releasing properties are available. However, these medications have disadvantages, as their effect is limited and gradually decrease with long-term usage, as known as the wearing-off phenomenon [5,6].

Since the 1990s, deep brain stimulation (DBS) has been used as a surgical therapy to improve motor symptoms associated with PD. Continuous stimulation of an electrospin fixed in the subthalamic nucleus, globus pallidus, or other regions has been shown to improve Parkinsonism by initiating and supporting the release of dopamine in these brain regions. Use of DBS enables patients to reduce their usual dosage of medication. It may be beneficial in improving the quality of life. In addition, reduction in drug dosage can decrease the risk of adverse effects due to medication [7].

However, DBS may elicit some adverse effects including psychiatric symptoms. Anxiety, depression, apathy, manic mood, cognitive impairment, and impulsiveness are well-known side effects of DBS [8-10]. Some studies have reported an increased incidence of suicide following DBS [11,12]. Although several initial prognostic examinations are performed on patients with PD eligible for DBS to uncover any predictors of psychiatric complications that may occur [13], it remains difficult to effectively identify patients with a high risk of DBS-induced psychosis [14]. On the other hand, there are some reports suggesting that DBS has beneficial effects upon psychiatric symptoms such as depression in PD patients [10,15]. It remains

controversial regarding the longitudinal effect of DBS on their mental state [16,17].

Therefore, we conducted an observational study to clarify the risk factors for psychiatric complications in PD patients underwent DBS.

Methods

We conducted a naturalistic non-controlled observational study on patients with PD who would be subjected to DBS. The inclusion criteria are shown below. Patients in whom all criteria were satisfied were included in the study.

- Adult patients with motor symptoms due to PD
- Hospitalized at Chiba University Hospital to be evaluated for indication of DBS
- The exclusion criteria were as follows:
- Have been diagnosed with dementia
- An apparent risk of suicide

A specialized psychiatrist interviewed all participants to obtain information on any past and/or current psychiatric symptoms, as well as the family history and past episodes of mental disorders. Meanwhile, some specialized physicians assessed the physical condition and motor function of the participants using the Unified Parkinson's Disease Rating Scale (UPDRS), part 3 [18]. Some occupational therapists also assessed cognitive function with the Mini-Mental State Examination (MMSE) and a bedside Frontal Assessment Battery (FAB). Based on the results of the medical examination, the multidisciplinary medical team composed of some physicians, a neurosurgeon, a psychiatrist, nurses, occupational therapists, and psychotherapists discussed the therapeutic strategy. Any psychiatric morbidities in the participants were taken into consideration of the decision making.

The daily dosage of anti-PD drugs prescribed to participants were calculated (Table 1) based on past references [19-22]. The DBS was performed by a specialized neurosurgeon based on the discussion by the multidisciplinary medical team. Bilateral STN-DBS was adopted unless other methods were preferable for the patient. Participants were reassessed at three months and one year following DBS. Medication for each patient was continuously regulated by a doctor-in-charge regardless of whether DBS was performed. Finally, we attempted to identify the risk factors potentially influencing to the psychiatric symptoms. We divided the participants into three groups according to the change of their mental state; worsened, no change, and improved. Then we compared some variables including demographic and clinical data in each group with statistics. Fisher's exact test and one-way analysis of variance were adopted for an exploratory analysis. The data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). $P<0.05$ was deemed as the level of statistical significance.

Name of drugs	Equivalent rate
Amantadine	100
Bromocriptine	15
Capergoline	2
Droxidopa	100
Entacapone	20
Levodopa	100
Pergolide	1.5
Pramipexole	1.5
Ropinirole	9
Selegiline	30
Talipexole	1.6
Trihexyphenidyl	4

Table 1: Equivalent rates of anti-Parkinson drugs.

Ethical Issues

We explained the study with a written protocol paper to the potential subjects. Only the patients who provided written informed consent to participate in this study were included. We reported the contents of this study to the Ethical Council of the Graduate School of Medicine at Chiba University in advance, and the council permitted us to conduct this study.

Results

A total of 44 patients participated in this study from April 2009 to December 2013; 20 were men, and 24 were women. Twelve patients were initially excluded from the analysis for the reasons below; one by being misdiagnosed, seven by canceling DBS, two by methods other than bilateral STN-DBS, and two by lack of important information. Thus, a total of 32 PD patients, of which 17 were men and 15 were women, were initially included in the analysis. The mean age at PD onset was 53.1 ± 7.1 (mean ± standard deviation; same as above) years, and the mean age at DBS surgery was 65.0 ± 6.6 years. Seven participants had relatives with PD. All 32 participants had severe motor symptoms related to PD, which interfered with their daily life activities.

The mean UPDRS part 3 score was 18.1 ± 7.0 at the on-phase and 42.3 ± 12.1 at the off-phase of anti-PD drugs. The mean MMSE and FAB scores were 28.6 ± 1.9 and 16.3 ± 1.8, respectively. The mean anti-PD drug dosage with an L-DOPA equivalent was 2305.6 ± 1613.3 mg/day. Three participants had been prescribed antipsychotics before initial assessment to treat some psychiatric symptoms. Eighteen participants had experienced some psychotic symptoms (hallucination and/or delusion). Nineteen patients were suffering from dopamine dysregulation syndrome (DDS) upon initial assessment. Five participants suffered from tranquilizer dependency, eight exhibited addictive gambling behavior, ten experienced mood swings, and seven were found to be in a depressive state upon initial assessment. Thirteen participants were diagnosed with some mental disorders based on the criteria in the International Classification of Disease, 10th edition (ICD-10) at the time of assessment. Diagnosed mental disorders were as follows: Delirium not superimposed on dementia, so described (F05.0), Organic delusional disorder (F06.2; three participants), Organic mood disorder (F06.3; two participants), Mild cognitive disorder (F06.7), Organic personality disorder (F07.0), Adjustment disorder (F43.2), Nonorganic insomnia (F51.0), Personality disorder unspecified (F60.9), Other habit and impulse disorder (F64.8), and dual diagnoses with Bipolar affective disorder (F31.7) and Mild mental retardation (F70).

A total of 26 patients were reassessed at three months after surgery, and 19 participants were re-assessed at one year. The mean UPDRS part 3 score at the on-phase decreased to 11.8 ± 6.8 at three months with statistical significance (bilateral paired-T-test with Last Observation Carried Forward method [LOCF], P=0.0049), but slightly rose to 13.9 ± 10.0 at one year after DBS. In contrast, the mean anti-PD drug dosage was 993.4 ± 1087.3 mg/day at three months, which was reduced from the baseline with statistical significance (bilateral paired-T-test with LOCF, P=0.00027). At one year after DBS, the mean dose was 662.6 ± 425.1 mg/day at one year after DBS (Figure 1).

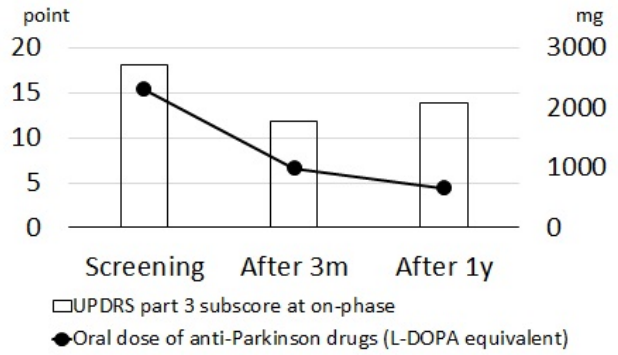

Figure 1: change in symptoms and medication.

A total of 16 participants (61.5%) was experiencing some psychiatric symptoms at three months, of which 12 were considered to be influenced by the DBS, because of these two reasons: (1) these symptoms had not appeared in each patient until DBS was performed, and (2) these symptoms subsided after weakening the level of stimulation by a neurosurgeon. Each symptom was identified as follows: depressive symptoms 4, mood swing 3, impulsiveness 3, hypomanic symptoms 1, and anxiety 1. In contrast, some improvement in psychiatric symptoms was observed in six participants.

After one year, 9 of the 19 participants (47.4%) was experiencing some psychiatric symptoms, of which 7 were considered to be influenced by the DBS. Each symptom was identified as follows: depressive symptoms 1, mood swing 1, impulsiveness 3, hypomanic symptoms 1, mild dependency to anti-PD drugs 1. In addition, mild cognitive impairment occurred in one participant that was uncertain due to DBS. Psychiatric symptoms were worsened in six participants compared to the three months assessment, whereas improvement in psychiatric symptoms was observed in six participants.

In comparison of three groups followed by the change of mental status, there were no significant findings for the variables we gathered in this case series (Tables 2 and 3). At one year after DBS, the existence of DDS at the screening was correlated to the change in psychiatric symptoms with statistical significance (Fisher's exact test, P=0.020). Thus, patients with DDS before DBS were likely to deteriorate their psychiatric symptoms. No other factors were identified as a predictor of mental state outcome.

Variables	Worsened group	Unchanged group	Improved group	P value
Sex	Male 5, Female 7	Male 5, Female 3	Male 3, Female 3	NS*
Age at onset PD	54.67 ± 5.38	53.88 ± 11.36	50.67 ± 5.39	NS**
Age at DBS surgery	66.83 ± 4.99	65.13 ± 10.20	63.83 ± 4.36	NS**
Relatives with PD	Yes 5, No 7	Yes 2, No 6	Yes 0, No 6	NS*
UPDRS part 3 score at the on-phase	19.82 ± 6.71	17.71 ± 7.74	15.00 ± 6.93	NS**
UPDRS part 3 score at the off-phase	45.58 ± 15.98	40.38 ± 9.86	38.17 ± 11.03	NS**
MMSE	29.08 ± 1.16	27.29 ± 2.81	28.17 ± 2.14	NS**
FAB	16.25 ± 1.42	15.43 ± 2.64	16.50 ± 1.38	NS**
Psychotic symptoms	With 7, Without 5	With 3, Without 5	With 5, Without 1	NS*
Dopamine dysregulation syndrome	With 8, Without 4	With 3, Without 5	With 6, Without 0	NS*
Tranquilizer dependency	With 4, Without 8	With 0, Without 8	With 1, Without 5	NS*
Addictive gambling behavior	With 5, Without 7	With 2, Without 6	With 1, Without 5	NS*
Mood swing	With 5, Without 7	With 1, Without 7	With 2, Without 4	NS*
Depressive state	With 1, Without 11	With 1, Without 7	With 2, Without 4	NS*
anti-PD drug dosage with a L-DOPA equivalent	2200.93 ± 1827.02	2591.67 ± 1724.63	2231.94 ± 1542.51	NS**

Table 2: Comparison of three groups at the 3 months after surgery.

Variables	Worsened group	Unchanged group	Improved group	P value
Sex	Male 3, Female 3	Male 4, Female 3	Male 1, Female 5	NS*
Age at onset PD	51.17 ± 10.42	54.57 ± 7.87	51.83 ± 4.71	NS**
Age at DBS surgery	63.17 ± 8.57	67.71 ± 7.34	64.83 ± 3.97	NS**
Relatives with PD	Yes 1, No 5	Yes 0, No 7	Yes 2, No 4	NS*
UPDRS part 3 score at the on-phase	18.60 ± 8.41	17.86 ± 7.99	23.00 ± 3.32	NS**
UPDRS part 3 score at the off-phase	38.17 ± 11.46	39.00 ± 11.87	51.00 ± 20.55	NS**
MMSE	27.33 ± 2.88	28.71 ± 1.70	28.50 ± 1.98	NS**
FAB	15.33 ± 1.63	16.57 ± 1.81	15.50 ± 2.17	NS**
Psychotic symptoms	With 5, Without 1	With 5, Without 2	With 3, Without 3	NS*
Dopamine dysregulation syndrome	With 5, Without 1	With 6, Without 1	With 1, Without 5	.020*
Tranquilizer dependency	With 1, Without 5	With 1, Without 6	With 1, Without 5	NS*
Addictive gambling behavior	With 2, Without 4	With 1, Without 6	With 1, Without 5	NS*
Mood swing	With 3, Without 3	With 1, Without 6	With 2, Without 4	NS*
Depressive state	With 2, Without 4	With 1, Without 6	With 0, Without 6	NS*
anti-PD drug dosage with a L-DOPA equivalent	2169.91 ± 1888.00	2626.19 ± 1732.55	1809.72 ± 1660.43	NS**

Table 3: Comparison of three groups at the 1 year after surgery.

Discussion

We conducted an observational study in a clinical setting to elucidate the risk factors for psychiatric complications associated with DBS for patients with PD. As a result, DDS was suspected to be a risk factor for worsening mental state in the longitudinal course.

DDS has an adverse impact on the daily life in PD patients. DBS is considered to be a desirable therapeutic option for the patients with DDS [23]. However, our result suggests that we have to be cautious to the onset or worsening of psychiatric symptoms when adopting DBS to patients with DDS.

Other than this result, some interesting facts were suggested through this study. First, almost half of the participants were diagnosed as some mental disorders with a clinical interview at the initial assessment, although they had been evaluated by the doctor-in-charge previously. Psychiatric complications such as depression and impulsivity are frequently seen in patients with PD [3,24,25], and patients with cognitive and/or behavioral problems are often contraindicated for DBS [26]. The participants of this study had been considered as good candidates for DBS by the doctors-in-charge. Thus, it is possible that some psychiatric symptoms in the participants had been overlooked by doctors-in-charge. This fact suggests that more detailed assessment of the patients is needed when considering introducing a patient with PD for DBS.

Second, to be paradoxical for the fact we mentioned above, some participants showed remarkable improvement of mental status after the surgery, especially in those without DDS. Indeed, there are some previous reports describing the effect of DBS on the mental status of the patients with PD [15,27,28]. Some reasons for their recovery are estimated. Regulating of dopamine release in the brain can stabilize the mood swing [29]. Some studies suggest the direct effects of DBS on mental disorders [30]. In addition, it is likely that the decrease in the amount of dopaminergic medication in accordance with DBS devoted to stabilization of their mood and/or psychotic symptoms [31,32].

Previous studies suggest the relationship between psychiatric complications after DBS and some risk factors. For instance, impulse control disorders are likely to occur in male patients with early onset of PD, history of alcoholism and gambling behaviors [13]. Psychiatric disturbance at baseline is also suggested to be a risk [33]. We included these variables into the analysis, but failed to replicate their results, perhaps due to the small sample size.

In spite of many studies suggesting impaired executive functions in PD patients, it seems not to be directly associated with psychiatric symptoms in PD [34]. In our study, there was no correlation found between worsening of psychiatric symptoms and cognitive functions measured with MMSE and FAB. Considering that patients with severe deficit of executive functions were not included in this study, this result was not surprising. It remains uncertain regarding the risks of psychiatric complications with DBS for the patients with highly deteriorated cognitive function.

Many studies have warned about suicidal ideation and suicide in the patients after DBS [11,12,35,36]. The suicide rate is estimated as 0.16% or 0.5% [11,36]. On the other hand, there is a randomized controlled trial with a large sample size reporting that DBS did not raise the risk of suicidal behaviors compared to medication [37]. In the present study, no participants, including ones dropped out from our study, experienced severe suicidal thoughts in the term of observation. Perhaps doctors-in-charge excluded the patients at risk of suicide from

the candidate of DBS in advance. Nonetheless, we have to be cautious about monitoring the risk of suicide continuously. Careful observation by a multidisciplinary team will reduce the risk of undesirable outcomes [28].

There were few participants with PD relatives in the improved group in this study. It would be suggestive, although failing to prove their relationship with statistical significance, since some types of PD involve heritable factors [38], as certain genes have been suggested to cause inherited forms of PD [39]. They may be vulnerable to organic stress caused by DBS. Few reports describe DBS outcomes of the patients with a familial form of PD. Further investigation including genetic tests with a large sample size should be performed to discuss this matter.

The main limitation of our study is selection bias of the participants. Only the patients who regularly visit our hospital could be included. As a naturalistic study, some participants were dropped out from the follow up for personal reasons such as moving home. The small sample size also limited the statistical power. A multi-centered prospective cohort study with a controlled group is necessary for identifying the predictive factors of alteration in psychiatric symptoms after DBS.

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