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BRIEF COMMUNICATION

Modified Ratio of Tremor/Postural Instability Gait Difficulty Score as an Indicator of Short-Term Outcomes of Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

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ABSTRACT

Objective The outcomes of motor and nonmotor features of Parkinson's disease (PD) following deep brain stimulation (DBS) vary among its subtypes. We tested whether preoperative motor subtyping using the modified tremor/postural instability and gait difficulty ratio (T/P ratio) could indicate the short-term motor, nonmotor and quality of life (QOL) outcomes of subthalamic nucleus (STN) DBS.

Methods In this prospective study, 39 consecutive STN DBS patients were assessed in the drug-OFF state before surgery and subtyped according to the T/P ratio. Patients were reassessed 6 months after surgery in the stimulation ON-drug-OFF state, and the percentage changes in motor, nonmotor and QOL scores (Parkinson's Disease Quality of Life Questionnaire [PDQ-39]) were calculated.

Results The modified T/P ratio was moderately and positively correlated with the percentage change in the Unified Parkinson's Disease Rating Scale III score in the OFF state, the sum of cardinal motor signs, the Non-Motor Symptom Scale score, and QOL (PDQ-39).

Conclusion Preoperative PD motor subtyping can be used as an indicator of the short-term outcomes of STN DBS in PD patients.

Keywords Parkinson's disease subtypes; Deep brain stimulation; Tremor/postural instability and gait difficulty ratio; Motor and nonmotor outcomes.

INTRODUCTION

Parkinson's disease (PD) is a heterogeneous disorder with varied clinical manifestations and pathophysiological mechanisms.[1] Various PD subtyping methods have been proposed to predict the course of PD and the outcomes of therapies. Based on dominant motor phenotype derived from the scores of the Unified Parkinson's Disease Rating Scale (UPDRS), PD can be categorized into tremor-dominant (TD), postural instability and gait difficulty (PIGD), and indeterminate (IT) subtypes. In addition to characterizing motor features, this method of classification was found to be suitable to study nonmotor symptoms.[2] Com-

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pared with those of the TD subtype, the severity of axial features, impaired postural reflexes, freezing of gait, nonmotor symptom burden, rate of cognitive decline, and progression of disease are greater in the PIGD subtype.[3]

The outcomes of PD following deep brain stimulation (DBS) are influenced by motor subtypes. Better motor outcomes following both subthalamic nucleus (STN) and globus pallidus internus DBS in TD subtype were reported in two studies.[4,5] In contrast, a retrospective study reported greater motor improvement in the akinetic rigid subtype.[6] Nonmotor outcomes were reported to be better in the PIGD subtype.[7] These inconsistencies in outcomes could be due to differences in the subtyping methods, the baseline severity of motor and nonmotor symptoms, and the variable progression of the dominant motor features.

We hypothesized that the pre-DBS-modified ratio of tremor/PIGD scores is an indicator of STN DBS outcomes. Unlike previous studies, we tested the ability of motor subtyping to indicate both motor and nonmotor outcomes at 6 months following STN DBS.

MATERIALS & METHODS

Between January 2021 and December 2022, 39 patients who fulfilled standard eligibility criteria for DBS underwent bilateral STN DBS in our hospital and all were available for follow up at 6 months post DBS. Uniform, protocol-based assessments were performed 2 weeks before DBS and 6 months after DBS. The study was approved by the Institutional Ethics Committee (AM/EC/238-2022), and written informed consent was provided by the patients.

Pre- and post-DBS assessments

Pre-DBS assessments were conducted in the drug OFF (after overnight dopaminergic drug withdrawal) and drug ON (1 hour after the morning dose of dopaminergic drugs) states. Post-DBS assessments included stimulation-ON and both drug OFF and drug ON states. Motor subscores were calculated from the UPDRS III OFF score. Scores were calculated for the following symptoms: tremor (sum of items 20−21); rigidity (item 22); bradykinesia (sum of items 23−26 and 31); the sum of tremor, rigidity, and bradykinesia (T+R+B); and axial features (sum of items 27, 30). The Non-Motor Symptom Scale (NMSS), Parkinson's Disease Fatigue Scale, Parkinson's Disease Sleep Scale (PDSS), King's Parkinson's Disease Pain Scale, Beck Depression Inventory (BDI), Frontal Assessment Battery (FAB), Montreal Cognitive Assessment (MoCA), and Parkinson's Disease Quality of Life Questionnaire (PDQ-39) summary indices were used to derive specific scores. The percentage change in scores 6 months after DBS was calculated using the following formula:

$$\frac{\text{preoperative drug OFF score-postoperative stimulation ON drug OFF score}}{\text{preoperative drug OFF score}} \times 100.$$

Tremor and PIGD scores were calculated from pre-DBS drug-OFF scores of these items in UPDRS II and III as previously described.[8] Briefly, the tremor score is the mean score of 8 items: item 16 in the UPDRS II and items 20 (5 subitems) and 21 (2 subitems) in the UPDRS III. The PIGD score is the mean of 5 items: items 13, 14, and 15 in the UPDRS II and items 29 and 30 in the UPDRS III. The tremor/PIGD ratio (T/P ratio) was then calculated for each patient. The pre-DBS T/P ratio in the drug OFF state was transformed to the modified T/P ratio, which was calculated as follows:

$$\log\sqrt{\frac{\text{tremor score}+0.01}{\text{PIGD score}+0.01}}.$$

This transformed score was used as a continuous variable because it permits the inclusion of all the patients for correlation analysis, including those with tremor scores, PIGD scores or both scores of 0, as reported earlier.[9]

The outcome measures included correlations between the pre-DBS-modified T/P ratio and percentage changes in motor, nonmotor and quality of life (QOL) scores.

Surgical procedure

Surgery was performed as described in a previous study.[10] We used 3T magnetic resonance imaging for STN localization, intraoperative, 5-channel microelectrode recording, and macrostimulation followed by the placement of quadripolar electrodes (model 3389) and an implantable pulse generator (Medtronic). The contact with the widest therapeutic window and the best clinical benefit was chosen for chronic stimulation on each side.

Statistical analysis

Continuous variables are expressed as means±standard deviations. Pre- and post-DBS scores were compared by paired *t*-tests, with *p* values less than 0.05 indicating significance. The median values of the percentage changes in the scores of the outcome variables were calculated. Pearson's correlation was used to test the association between the modified T/P ratio and the percentage change in clinical score. The Mann−Whitney U test was used to compare the medians of percentage changes between the groups. The degree of correlation was considered based on *r* value: An *r*-value of 0.39 or less was considered low, *r* between 0.4 and 0.59 was considered moderate, and an *r*-value of 0.6 or greater was considered high.

RESULTS

All 39 patients completed the 6-month follow-up visit. The mean age at surgery was 60.7±8.5 years, and the mean disease duration was 9.7±4.3 years. At the pre-DBS assessment, the subtypes of 31 (79.5%), 6 (15.4%), and 2 (5.1%) patients were classified as PIGD, TD, and IT, respectively.

The mean pre-DBS and 6-month post-DBS scores are shown in Table 1. The pre-DBS scores of the variables among the subtypes are shown in Supplementary Table 1 (in the online-only Data Supplement).

Correlations of the modified T/P ratio with the percentage of improvement in motor, nonmotor and QOL scores

The correlations between the modified T/P ratio and percentage change in the scores of the variables at 6 months after DBS and comparisons of medians between the groups are shown in Table 2. A positive and significant correlation was observed between the T/P ratio and percentage changes in the UPDRS II, III, tremor, axial, T+R+B, NMSS, and PDQ-39 scores. A negative correlation was observed between the T/P ratio and the percentage changes in the PDSS, BDI, MoCA, and FAB scores, but not significant.

Table 1. Comparison of the mean pre and post-DBS motor and nonmotor scores (*n*=39)

	Pre-OP	Post-OP	*p* value
UPDRS I OFF	2.62±2.38	1.38±2.02	0.009
UPDRS II OFF	20.69±6.31	8.67±5.89	<0.001
UPDRS III OFF-total	39.41±14.41	12.69±10.46	<0.001
UPDRS III tremor OFF	4.10±4.14	0.41±0.72	<0.001
Bradykinesia OFF	17.92±6.93	7.15±5.75	<0.001
Rigidity OFF	6.23±2.92	0.56±1.00	<0.001
Axial OFF	6.36±4.02	2.54±3.18	<0.001
UPDRS III OFF-T+R+B	28.26±10.65	8.13±6.33	<0.001
UPDRS IV part A+B	5.62±2.14	1.64±1.60	<0.001
UPDRS V OFF	3.21±1.08	1.67±1.11	<0.001
UPDRS VI OFF	49.74±23.00	83.08±18.38	<0.001
LEDD	786.69±265.87	340.13±256.43	<0.001
NMSS-total	60.41±47.92	29.95±29.53	0.001
PDFS-16	48.51±16.56	33.56±15.77	<0.001
PDSS	105.38±23.96	133.23±17.31	<0.001
KPPS	11.36±14.20	5.87±5.97	0.028
PDQ-39	64.28±20.12	32.49±19.76	<0.001
MoCA	25.62±2.83	25.67±3.15	0.910
BDI	10.72±6.42	6.36±4.46	<0.001
FAB	16.92±1.38	16.08±2.96	0.043

Values are presented as mean±standard deviation.
DBS, deep brain stimulation; Pre-OP, Pre-operative; Post-OP, Post-operative; UPDRS, Unified Parkinson's Disease Rating Scale; T+R+B, tremor, rigidity, and bradykinesia; LEDD, levodopa equivalent daily dosage; NMSS, Non-Motor Symptom Scale; PDFS-16, Parkinson's Disease Fatigue Scale; PDSS, Parkinson's Disease Sleep Scale; KPSS, King's Parkinson's Disease Pain Scale; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; FAB, Frontal Assessment Battery.

DISCUSSION

In the present study, we found that the modified T/P ratio calculated before DBS was positively associated with total motor score (UPDRS III OFF), NMSS, and QOL changes at 6 months after STN DBS. A lesser improvement in these scores was indicated in the short term by a lower ratio in those with prominent PIGD features.

Pre-DBS motor subtype and clinical improvement in motor symptoms

The modified T/P ratio was strongly correlated with the percentage change in UPDRS III OFF score, and axial scores which indicated that PD patients with higher tremor scores had better improvement in overall motor symptoms, including axial features, than those with higher PIGD scores. This finding is similar to that of a previous report.[4] A lower T/P ratio, as in the PIGD subtype, is associated with less favorable outcomes in both overall motor and axial scores. The positive correlation between the percentage change in motor variables and the modified T/P ratio was not dependent on the baseline score (Supplementary Table 2 in the online-only Data Supplement).

Pre-DBS motor subtype and improvement in nonmotor symptoms and QOL

We found a moderate correlation between the modified T/P ratio and the total NMSS and PDQ-39 scores, suggesting that PD patients with prominent tremor in the preoperative period can be expected to have greater improvement in the overall severity of nonmotor symptoms and QOL. Our findings contrast with those of a study by Jost et al.,[7] which reported greater improvements in NMSS scores and QOL scores in patients with the PIGD subtype than in patients with the TD subtype. Conversely, our findings are similar to those of the study by Katz et al.,[4] who showed greater improvement in the QOL (PDQ-39 score) among patients with the TD subtype than among those with the PIGD subtype after DBS. This difference could be due to the differences in the baseline severity of symptoms and the number of patients with the TD subtype in the two studies. We found only a weak association between the modified T/P ratio and improvements in depression and cognitive scores.

The response of individual symptoms to DBS is known to vary

Table 2. Correlation between percentage change in scores of clinical variables and modified T/P ratio and comparison of percentage change grouped by median modified T/P ratio

	Modified T/P ratio		Modified T/P ratio ≤median (*n*=19)	Modified T/P ratio >median (*n*=20)	*p* value‡	Modified T/P ratio total (*n*=39)
	Pearson correlation (*r*)	*p* value†	Median (IQR)	Median (IQR)		Median (IQR)
UPDRS I	0.021	0.900	75 (50 to 100)	0 (-100 to 90)	0.050	50 (-20 to 100)
UPDRS II	0.511*	0.001	50 (22.2 to 68.8)	67.7 (58.4 to 86.6)	0.005*	60 (42.9 to 80.8)
UPDRS III	0.425*	0.007	57.6 (34.8 to 79.5)	83.1 (61.5 to 93.5)	0.002*	72.5 (53.8 to 87.2)
UPDRS III tremor	0.482*	0.002	100 (0 to 100)	100 (83.7 to 100)	0.322	100 (75 to 100)
Bradykinesia	0.297	0.067	58.8 (31.8 to 63.6)	81.4 (38.6 to 92.6)	0.009*	63.2 (38.1 to 81.8)
Rigidity	0.233	0.154	100 (80 to 100)	100.0 (87.5 to 100)	0.478	100 (87.5 to 100)
Axial	0.435*	0.006	66.7 (21.4 to 80)	100 (61.7 to 100)	0.016*	77.8 (50 to 100)
UPDRS III-T+R+B	0.443*	0.005	61.5 (50 to 77.3)	79.9 (63.8 to 94.7)	0.002*	76.3 (56.5 to 87.5)
UPDRS IV part A+B	0.259	0.112	44.4 (33.3 to 83.3)	87.5 (76.7 to 100)	0.003*	81.8 (40 to 100)
UPDRS V	0.545*	<0.001	33.3 (20 to 50)	55.0 (42.5 to 100)	0.001*	50.0 (33.3 to 66.7)
UPDRS VI	0.049	0.765	-60 (-200 to -3.3)	-50 (-80 to -28.6)	0.569	-50 (-150 to -28.6)
LEDD	0.168	0.306	47.5 (36 to 81)	63.1 (52.7 to 85)	0.184	60.0 (43.5 to 81.2)
NMSS-total	0.330*	0.040	62.5 (-3 to 78)	63.1 (8.4 to 71.2)	0.923	63.0 (6.4 to 74.1)
PDFS-16	0.229	0.161	15.0 (-9.2 to 40.6)	38.5 (3.9 to 59)	0.175	31.4 (0 to 53.8)
PDSS	-0.258	0.113	-21.4 (-33.7 to -6)	-21.2 (-31.5 to -11)	0.687	-21.4 (-31.5 to -8.1)
KPPS	0.019	0.910	-40.0 (-150 to 91.7)	45.2 (-175 to 90.6)	0.835	33.3 (-150 to 91.7)
PDQ-39	0.362*	0.023	39.7 (19 to 73)	62.4 (45.9 to 76)	0.127	59.1 (32.1 to 73.3)
MoCA	-0.174	0.291	0.0 (-7.4 to 6.7)	0.0 (-8.6 to 3.4)	0.728	0.0 (-8.3 to 4.3)
BDI	-0.028	0.864	61.5 (20 to 75)	25.8 (-18.8 to 54.4)	0.084	50.0 (0 to 66.7)
FAB	-0.281	0.083	0.0 (-5.9 to 16.7)	0.0 (0 to 5.6)	0.857	0.0 (0 to 6.7)

Modified T/P ratio, median (IQR)=-0.185 (-0.484 to -0.244).
*significant at the 0.05 level (2-tailed); †Pearson correlation *p* value; ‡Mann–Whitney U test.
T/P ratio, tremor/postural instability and gait difficulty ratio; IQR, interquartile range; UPDRS, Unified Parkinson's Disease Rating Scale; T+R+B, tremor, rigidity, and bradykinesia; LEDD, levodopa equivalent daily dosage; NMSS, Non-Motor Symptom Scale; PDFS-16, Parkinson's Disease Fatigue Scale; PDSS, Parkinson's Disease Sleep Scale; KPSS, King's Parkinson's Disease Pain Scale; PDQ-39, Parkinson's Disease Quality of Life Questionnaire; MoCA, Montreal Cognitive Assessment; BDI, Beck Depression Inventory; FAB, Frontal Assessment Battery.

among PD patients. A greater improvement in tremor scores than in axial scores has been reported.[11] The exact reasons for such differences are not fully understood. They could be due to differences in the circuits subserving these symptoms and their distribution within the volume of tissues stimulated,[12,13] and their responsiveness to stimulation parameters, such as frequency and pulse width.

The smaller improvements in motor, nonmotor and QOL scores in those with prominent PIGD features (lower modified T/P ratios) are in line with earlier reports.[4,14] The novelty of this study is that the relationships between pre-DBS-dominant motor features, described as the modified T/P ratio, and improvements in motor and nonmotor symptoms and QOL following STN DBS were demonstrated in the same cohort of patients.

Study limitations include the small sample size, short-term follow-up and predominance of the PIGD subtype in the pre-DBS assessment. The predominance of the PIGD subtype in the DBS cohort may be due to the appearance of more axial features with the progression of PD in these patients rather than selection bias, because the cohort included all consecutive patients who underwent DBS during the study period. The dynamic nature of PD subtypes is considered to reflect a disease continuum that is influenced by many factors.[15] A 6-month follow-up of cognition can reveal only immediate impact of DBS on cognition, and longer follow-up is needed to understand differences in the cognitive outcomes of different motor subtypes.

We conclude that an assessment of the T/P ratio in the preoperative work-up of STN DBS may be useful in indicating the short-term outcomes of cardinal motor signs and overall improvements in the nonmotor symptoms and QOL. A lesser improvement in these domains can be expected if the T/P ratio is low, as in the PIGD subtype. Studies with larger sample sizes and longer follow-up periods are needed to confirm the value of pre-DBS motor subtyping in predicting the outcome of STN DBS.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.24175.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Asha Kishore, Chakradhar Reddy. Data curation: Chakradhar Reddy. Formal analysis: Manas Chacko. Funding acquisition: Asha Kishore. Investigation: Chakradhar Reddy, Harshad Chavotiya, Kanchana Pillai, Shejoy Joshua, Anup Nair. Methodology: Asha Kishore, Chakradhar Reddy. Project administration: Asha Kishore, Chakradhar Reddy. Supervision: Asha Kishore. Validation: Asha Kishore. Writing—original draft: Chakradhar Reddy. Writing—review & editing: Asha Kishore, Chakradhar Reddy.

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