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ORIGINAL ARTICLE - FUNCTIONAL NEUROSURGERY - MOVEMENT DISORDERS

Range of voluntary neck motility predicts outcome of pallidal DBS for cervical dystonia

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Abstract

Background The effectiveness of pallidal deep brain stimulation (GPi DBS) for cervical dystonia has been extensively described, but controversies exist about which prognostic factor is clinically useful. We previously reported that classification of tonic- or phasic-type cervical dystonia is useful for predicting clinical prognosis; however, the approach used by physicians to distinguish between the two types remains subjective.

Objective The aim of this study was to develop a prognostic factor of GPi DBS for cervical dystonia.

Methods By identifying distributions of range of motion scores between phasic- and tonic-type cervical dystonia, a new prognostic factor group was developed based on whether the patients could voluntarily move their head to the opposite side against dystonic motions. The prognosis for GPi DBS in the two groups was analyzed according to the time sequence.

Results Patients who were able to move their head past the midline had a better long-term prognosis after GPi DBS than did those who could not. In the early post-operative phase, there were no significant differences in the clinical outcomes between the two groups.

Conclusion A range of voluntary neck motility with respect to the midline is an objective factor that is useful in predicting the prognosis of patients with cervical dystonia. This result renders needs for future study addressing neuroplastic changes in the brain network caused by GPi DBS.

Keywords Deep brain stimulation · Cervical dystonia · Prognostic factor · Neuroplasticity

Introduction

Cervical dystonia is one of the most common types of focal dystonia [12]. Deep brain stimulation (DBS) of the globus pallidus internus (GPi) is a well-established surgical method for medically intractable cervical dystonia [16, 28, 32, 33]. Some patients receive significant effective therapeutic benefits from GPi DBS, with an improvement in dystonia up to 90%. However, the other patients show less favorable effects (~ 50%) [5, 30, 33]. If these differential outcomes could be predicted before surgery, the patients would be able to decide whether the operation is needed based on reliable expectations. Several predictive factors for GPi DBS outcomes have been suggested such as younger age, shorter disease duration, absence of fixed skeletal deformity, and TOR1 mutation [30, 33, 35]. However, reliable values for predicting the clinical outcomes of GPi DBS have yet to be determined [17, 22, 34].

We reported elsewhere the different clinical outcomes of both phasic- and tonic-type cervical dystonia after GPi DBS [5]. This difference reflects the dual effects of DBS, i.e., early and delayed benefits. The immediate effects on the oscillatory basal ganglia network lead to an early improvement of phasic-type dystonic movements [2, 5, 17]. A delayed effect of GPi DBS, involving a functional reorganization of the motor cortex and basal ganglia, also known as neuroplasticity change, requiring more time, was observed in both types of cervical dystonia [5, 33]. The criteria used to distinguish between phasic- and tonic-type cervical dystonia, however, are

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subjective and may be arbitrary [2, 5, 11, 33]. It is not appropriate to provide patients with information regarding a prognosis of their surgical outcome based on the subjective judgement of the physician. Therefore, the development of an objective prognostic factor is necessary to provide patients with a suitable opportunity to decide whether they should undergo GPi DBS. The goal of this study was to develop a prognostic factor that is clinically useful for predicting the surgical outcomes of GPi DBS.

Patients and methods

The local institutional review board for clinical studies approved the present study design (subject number, OC18RESI0108), and patient's consent was not required in this type of study. Consecutive 42 patients diagnosed with cervical dystonia underwent bilateral GPi DBS at our hospital between February 2011 and October 2017. Their inpatient and outpatient medical records were fully reviewed, and 3 of the 42 patients were excluded from this study. One patient lacked detailed clinical data of Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), and the other two patients were lost to follow-up shortly after the surgery. The remaining 39 patients were included in this study. The mean (± SD) age (year), disease duration (month), and follow-up duration after surgery (month) were 51.7 (± 10.2), 65.8 (± 62.9), and 52.7 (± 14.3), respectively.

A diagnosis of cervical dystonia was made by identifying the typical clinical features of the patients by the senior author (R.H.). The essential clinical features include involuntary contraction of the neck muscles, which results to abnormal posture, movement, and pain. Pain associated with abnormal neck movement was observed in all of the patients involved in this study, and a sensory trick was found in 34 patients (87.2%). Fixed skeletal deformities were excluded by obtaining plain X-ray images of cervical spine. Presence of DYT1 gene mutation was also examined, and no DYT1 mutation was found. Many patients complained that emotional stress or social relationships frequently cause a temporary deterioration of the symptoms of dystonia. These psychological components of cervical dystonia can sometimes be confused with a psychiatric disorder. Psychiatric and neurological consultations were also conducted to distinguish between other diseases with similar symptoms, such as epilepsy and Parkinsonism [14]. Our GPi DBS procedures are described in great details elsewhere [5]; therefore, the procedure is described briefly as follows.

Magnetic resonance images (MRI) were obtained after fixation of a Leksell stereotactic frame (Leksell Coordinate Frame, Elekta, Stockholm, Sweden) on the patient's skull. The best target in the GPi is believed to be at the posterolateral and ventral region. We estimate its location in 20–24 mm lateral, 0–5 mm anterior, and 0–5 mm ventral from the mid-commissural point. Microelectrode recording was performed with three-channel microelectrodes to determine the physiological target. High-frequency and high-amplitude single-cell activity was considered to be activities of the GPi neuron. Macrostimulation was then performed with intraoperative neurologic examinations to check for possible stimulation-induced side effect. After implantation of the DBS electrode, the final lead locations were confirmed via fluoroscopy. The implantation procedure for the pulse generator was performed just after the intracranial electrode implantation under general endotracheal anesthesia.

The TWSTRS score was determined before surgery (baseline) and at the different postoperative follow-ups (1, 3, 6, 12 months, and last follow-up), and a video recording was also obtained each time. The improvement rate of the TWSTRS score indicates an improvement percentage (%) of the score at the follow-up examinations compared with the score at baseline. While the TWSTRS severity score is determined by examining the degree of abnormal motions of the neck, the disability and pain scores are based on the patients' subjective reporting. At this point, the severity score is considered to be the most objective variable. For this reason, the severity score was adopted as a candidate for development of an objective prognostic factor.

Statistical analysis and grouping patients by objective factor

SPSS statistics (version 19, IBM Company) was used for all statistical analyses. Since in previous studies the clinical outcomes of GPi DBS for phasic-type cervical dystonia were shown to be different from those of the tonic-type, the initial step should involve searching for an item showing significant difference between the two phenotypes. Using an independent *t* test, the difference in the severity score between the phasic- and tonic-types of cervical dystonia was determined. Because this step involves a multiple comparison, the Bonferroni correction was applied (statistical significance was defined as $P < 0.005$) to avoid type I error. As a consequence, the "Range of motion" was the only item that yielded a statistically significant difference between the phasic- and tonic-type cervical dystonia (see Supplemental Table 1, which shows results of the independent *t* test for the severity items between phasic- and tonic-type cervical dystonia). The histogram of the range of motion score (Fig. 1) indicated that patients belonging to the phasic-type dystonia scored 0–2 points while patients with the tonic-type tended to be distributed over the entire score (0–4 points). Based on this observation, the patients were classified according to a range of voluntary neck motility with respect to the midline, which is 0° on the axial, coronal, and sagittal planes. One group named "Able to cross

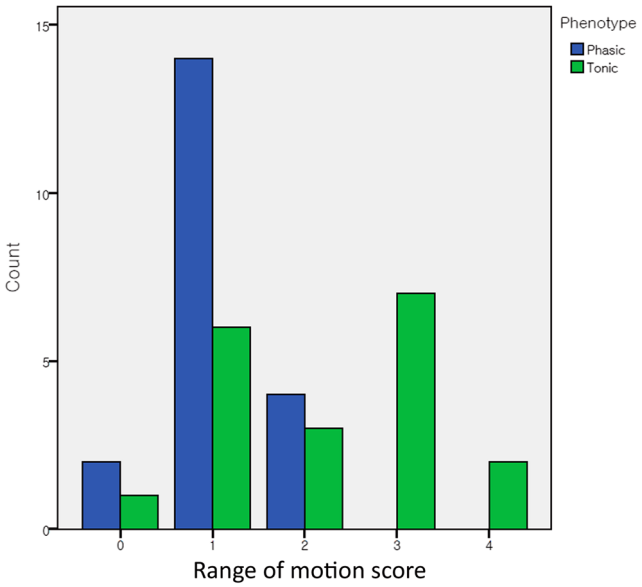

Fig. 1 Distribution patterns of the scores of "Range of motion" in patients with tonic- and phasic-type cervical dystonia. The "Range of motion" was the only item that yielded a statistically significant difference between the phasic- and tonic-type cervical dystonia. Based on this result, patients were classified according to the range of voluntary neck motility. One group was "Able to cross midline (AM) group," which is equivalent to "Range of motion" score of 0–1 point, and the other patients who scored 2–4 were grouped as "Unable to cross midline (UM)"

midline (AM)" indicated patients who could move their head voluntarily across the midline (> 0° of each plane) without any assistance. The other patients whose voluntary neck motion was limited to the midline (≤ 0° on each plane) were classified as the "Unable to cross midline (UM)" group.

Five time points were used to see the TWSTRS improvement rate (1, 3, 6, 12 months, and last follow-up). The measurements at each time point were compared using "repeated measures analysis of variance (rmANOVA)." The five levels of "Within-Subject Variables" (TWSTRS improvement rate) were compared using the "Between-Subject Factor" of the AM and the UM groups. Furthermore, to verify the effect of time on the different outcomes between the groups, the improvement rates at each time level were compared individually using "estimated marginal means". All analyses were performed with a two-tailed test and the significance level was defined as $P < 0.05$, unless otherwise specified.

Results

Mean age (SD), disease duration (SD), and the last follow-up (SD) were 51.7 (10.2) years old, 65.9 (62.9) months, and 52.7 (14.3) months, respectively. The characteristics of the patients in the two groups, the AM group (patients who were capable of moving their head from the affected side to the opposite side across the midline) and the UM group (patients who were unable to move their head across the midline), are summarized in Table 1. Mean age and gender distribution did not differ between the two groups, but mean disease duration and baseline TWSTRS scores were different.

Main findings

The improvement rate of the TWSTRS total score was significantly different between the AM group and the UM group (Table 2, rmANOVA, Between-Subjects Effects Test, $P = 0.011$). The AM group showed a better clinical outcome with an average TWSTRS total improvement rate of 73.9%, patients in the UM group had a 55.3% improvement at the last follow-up (Table 2, rmANOVA, Pairwise Comparisons, $P = 0.006$). The time levels having a significant difference were 3 months, 12 months, and the last follow-up (Fig. 2A), but there were no significant differences at the early (1 month and 6 months) follow-up evaluations between the two groups.

In the subscore analyses, the severity score showed a significantly better improvement rate in the AM group than in the UM group (rmANOVA, Between-Subjects Effects Test, $P = 0.004$). Similar to the TWSTRS total score, the difference in the severity improvement rate became clearer as the follow-up time after the GPi DBS increased (Table 2 and Fig. 2B). The mean (± SD) differences in the improvement rate between the two groups after 1 month, 6 months, and the last follow-up were 11.1% (± 8.3%), 18.3% (± 9.2%), and 21.5% (± 7.3%), respectively. No differences were noted in the remaining subscores. No statistical differences were found in the improvement rates of the disability and of the pain scores between the two groups (Fig. 2C and D and Table 2).

Post hoc analysis

There might be a relationship among other severity variables besides "Range of motion" and improvement rate, which might have influenced the above result. Therefore, the individual effects of each severity item on the improvement rate of the TWSTRS were examined at the last follow-up (univariate ANOVA). Statistical significance was set at $P < 0.005$ (Bonferroni correction). Only the "Range of motion" significantly affected the improvement rate of the TWSTRS after GPi DBS (Supplemental table 2, $P = 0.001$). No statistical connection could be found between the other severity items and the TWSTRS improvement rate.

Because baseline TWSTRS scores were significantly higher in the UM group than in the AM group, these worse baseline TWSTRS scores could cause worse outcome in this group. Therefore, correlation analyses were performed between baseline TWSTRS scores (severity, disability, and pain) and their improvement rates at the last follow-up (Pearson's

Table 1 Characteristics of patients

	Able to cross midline	Unable to cross midline	*P* value
No. of patients	23	16	
Age	50.6 ± 10.1	53.3 ± 10.3	0.424
Male:female*	8:15	8:8	0.509
Disease duration (month)	82.8 ± 75.0	41.4 ± 26.1	0.021
Phasic-:tonic-type*	16:7	4:12	0.007
Baseline TWSTRS	45.6 ± 8.5	53.5 ± 7.7	0.005
Follow-up duration (month)	56.0 ± 13.5	47.9 ± 14.5	0.082

*Chi-square test; Otherwise, independent *t* test

TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale

correlation). There was no significant correlation between the baseline TWSTRS scores and the improvement rates.

Locations of active contact and stimulation parameters, which might also be another compounding factor that affected the main findings, were compared between the AM and UM groups. The methods of verifying locations of the active contact and analyzing stimulation parameters were the same as those described in our previous studies [5, 13]. At the last follow-up, there were no significant differences in locations of the active contact between the AM and the UM groups. Mean (SD) amplitude, frequency, and pulse width at the last follow-up were 3.9 (0.64), 147.8 (25.2), and 83.3 (23.7), respectively. Comparison of these stimulation parameters, between the two groups, analyzed using the independent *t* test, showed no statistically significant differences. Mean (SD) amplitude, frequency, and pulse width of the AM group were 3.8 (0.79), 146.2 (19.7), and 81.0 (21.8), and those of the UM group were 3.9 (0.36), 148.9 (32.2), and 86.7 (26.4), respectively.

Discussion

We developed a novel prognostic factor for GPi DBS in patients with cervical dystonia using the finding that the range of motion was the objective preoperative factor statistically different between phasic- and tonic-type cervical dystonia. The new prognostic factor is the patients' ability to move their heads to the opposite side against the involuntary movement of the neck, which we identified by dividing the patients into the AM group and the UM group. The improvement rate in patients who were able to move their head beyond the midline (AM group) was significantly greater than in those who could not (UM group). The sequential comparison of the TWSTRS score between these two groups shows an interesting temporal pattern. While the difference in the early period was not significant between the two groups, the difference between the two groups became clearer over time. The most pronounced difference was found in the last follow-up (mean 51.7 months) comparison. These observations can be explained using a brain network model of dystonia and GPi DBS as follows.

Interpretation with the brain network model

In normal conditions, activation of the cerebral cortex for some motor tasks excites the medium-size spiny neuron (MSN) of the striatum, and its repetition gradually induces neuroplastic changes in the MSN [4, 10]. It encodes a rigid combination of a motor skill that once released can be completed independently of constant conscious oversight [10]. The striatum runs this motor skill via the GPi, and the GPi disinhibits its thalamic relay nucleus, i.e., ventral anterior (VA)/ventral lateral (VL) [6, 7, 24]. In patients with dystonia, excessive excitation of the corticostriatal projection causes an alteration in striatal synaptic plasticity (Fig. 3A) [4, 26]. This dysfunctional striatal MSN neuron relays its abnormal signals to the GPi, which in turn relays to the VA/VL [21, 25]. In this case, the normal resting activity of the GPi is substituted by abnormal signals (i.e., abnormal oscillation), which disinhibit the VA/VL even at the resting state [2, 19, 20]. Prolonged activation with this abnormal signal produces maladaptive neuroplasticity in the cerebral cortex via thalamocortical networks [1, 3, 4]. GPi DBS eliminates the abnormal oscillating patterns in the GPi, the local effect that is addressed by the classical DBS theory [8, 9]. Furthermore, GPi DBS alters network activity via facilitation of efferent and afferent myelinated axons near the DBS electrodes (Fig. 3B) [18, 27, 29]. Chronic stimulation with these bidirectional conductions could induce the reorganization of the abnormal neuroplasty in the cerebral cortex and the striatum [28, 33].

Many previous studies have reported that there are delayed benefits associated with GPi DBS in patients with dystonia, which is believed to reflect neuroplasticity changes triggered by a chronic stimulation of GPi DBS [30, 33]. The early benefits refer to a significant initial improvement in the severity of the dystonia within 1 month after GPi DBS, while the delayed benefit is an additional improvement in the clinical scores found between 6 months and 24 months after the initial improvement

Table 2 TWSTRS total and the severity/disability/pain score improvement rate at each follow-up time

Follow-up time	TWSTRS total score			Severity score		
	AM group	UM group	*P* value	AM group	UM group	*P* value
1 month	51.4% ± 5.1%	42.7% ± 6.1%	*0.281*	48.9% ± 5.3%	37.8% ± 6.4%	*0.192*
3 months	58.8% ± 5.1%	37.8% ± 6.1%	*0.012**	58.6% ± 5.0%	32.4% ± 6.0%	*0.002**
6 months	62.4% ± 5.5%	48.1% ± 6.6%	*0.102*	61.7% ± 5.8%	43.4% ± 7.0%	*0.053*
12 months	68.6% ± 4.8%	49.2% ± 5.8%	*0.015**	68.4% ± 5.0%	46.9% ± 6.0%	*0.009**
Last follow-up	73.9% ± 4.1%	55.3% ± 4.9%	*0.006**	73.1% ± 4.7%	51.6% ± 5.6%	*0.006**
rmANOVA			0.011*			0.004*

AM group, group of patients who are able to move their head past midline; *UM group*, patients who were unable to move their head past midline; *rmANOVA*, repeated measure analysis of variance

The italicized values indicate P-values of the pairwise comparisons between two groups at each follow-up time

Asterisks indicate that the results were significantly different between two groups

[33]. In this regard, the above results can be interpreted as follows; while the early benefit was found equally in both groups, the delayed benefit was more prominent in the AM group.

Limitation of this study

However, these interpretations still have to be proven in the future. These relationships between the nature of abnormal movement and degrees of abnormal neuroplasticity must be further revealed. For this, it is necessary to make dystonia animal models with isolated abnormal striatal or cortical neuroplasticity, but making such an animal model is still challenging for investigators up to date [23]. Transcranial magnetic stimulation is considered to be a very useful technique for determining levels of cortical neuroplasticity [4, 17, 28], and functional brain imaging techniques such as positron emission tomography and functional MRI may also be helpful [31]. These techniques can reveal different degrees of abnormal neuroplasticity in the striatum and the M1 between two groups in future studies.

Another question is the UM group also characterized by a significantly worse baseline TWSTRS score preoperatively

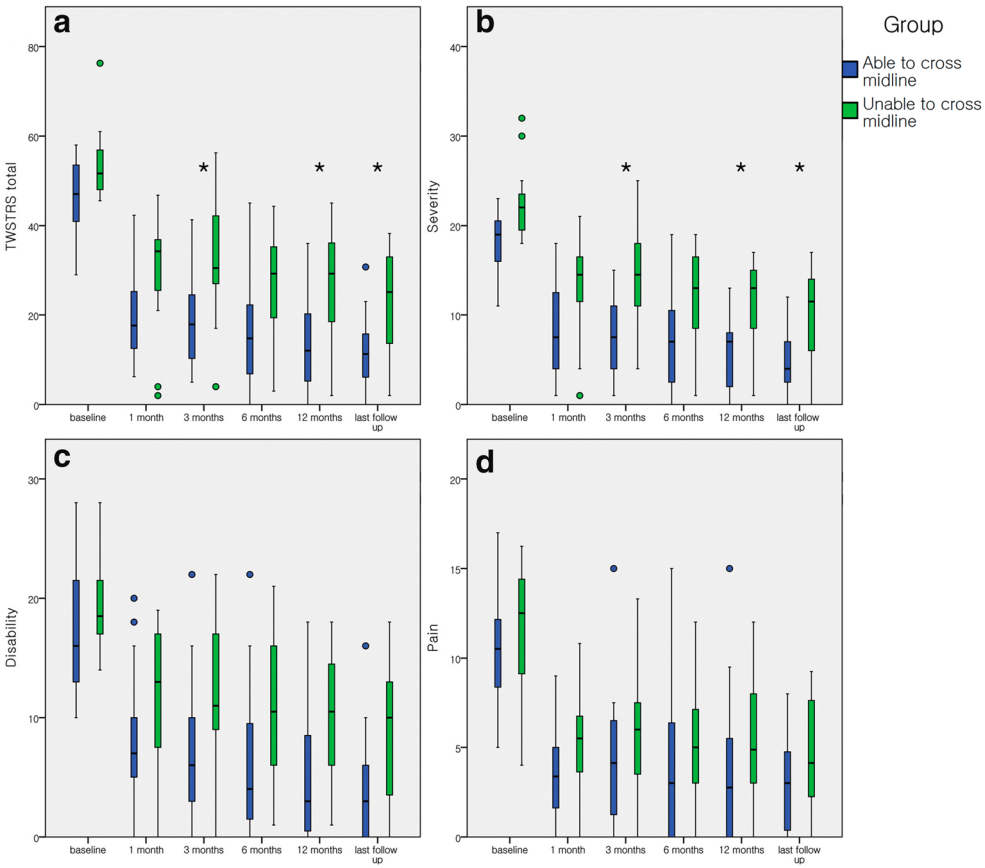

Fig. 2 Sequential changes in TWSTRS total and severity scores. In the late follow-up, an improvement rate of the TWSTRS total score is found to be greater in the AM group than in the UM group (A), and the severity score also showed the same patterns (B). However, significant differences are not found regarding the disability (C) and the pain (D) scores.

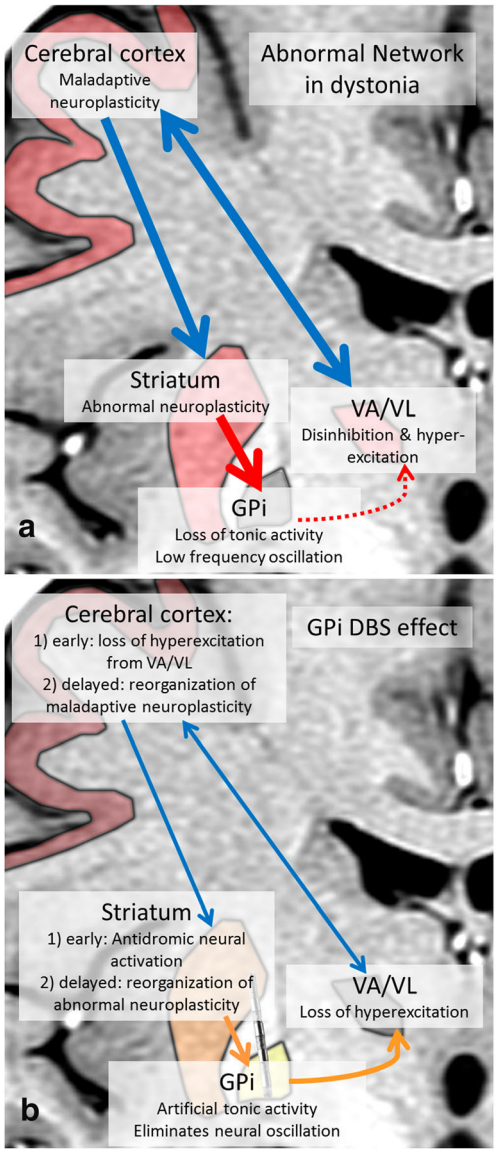

Fig. 3 Schematic illustrations of the brain network model. In patients with dystonia (A), excessive excitation of the corticostriatal projections (thick blue arrow) results in "loss of synaptic downscaling" in the striatum, which encodes dystonic movement rather than normal skilled movements. Dysfunctional striatal neurons relay their abnormal signals to the GPi (thick red arrow) and then to the VA/VL (broken red arrow). GPi DBS (B) alters network activity via orthodromic and antidromic conduction (yellow arrow). While orthodromic conduction suppresses VA/VL, antidromic conduction collides with the abnormal signals of the striatal medium spiny neurons. It improves over-excitation of the corticostriatal and thalamocortical networks (thin-blue arrow)

which could account for the worse outcome in this group. However, the baseline TWSTRS scores did not correlate with the improvement rate of TWSTRS scores, which were already mentioned in our previous article [5]. For patients of the AM group who were capable of turning their head, it seems that they would have a greater potential for a placebo effect as well since they have more capacity for normalization of their twisting at baseline. To eliminate such placebo effects, the patients were examined "single-blinded DBS off test" during parameter adjustment sessions in our outpatient clinic [13]. Two stages of symptom recurrence were always found, which were early phasic movement (within 1 min) and late tonic movement (within 30 min), which were also described by other researchers [15].

Because the present study was designed retrospectively, causal relationship could not be determined. Therefore, the results that the AM and the UM group show different clinical outcomes should be validated by future prospective studies. This study also had a risk of false-positive results which are coming from the multiple comparisons conducted in this study. To avoid this type I error, we applied the Bonferroni correction method. Finally, selection bias might exist because all patients included in this study were Korean and similar in terms of social, ethnic, and cultural aspects, a fact that may have affected the different neuropsychological processes associated with neuroplastic changes.

Advantage of this study

Even with these limitations described above, the present study has an advantage, i.e., the prognostic factor itself that we developed. Examining the ability of patients with cervical dystonia to turn their head against dystonic movement is quite easy and therefore clinically useful. Another advantage of this study is the homogeneity of the patients included in this study. Patient selection and targeting were performed by the senior author (R.H.), and all surgical procedures and stimulation parameter adjustments were performed by the junior author (M.C.), and detailed procedures were described elsewhere [5, 13]. Finally, this article provides an integrative view of cervical dystonia, including an analysis of the sequential long-term outcomes of GPi DBS, the introduction of the concept of the abnormal network of dystonia.

Conclusion

Among patients with cervical dystonia, those who were able to move their head to the side opposite that of the dystonic motion showed better long-term clinical outcomes after GPi DBS than patients who were not. Based on this observation, we developed a new prognostic factor, "range of voluntary neck motion to the opposite side." This variable can be easily examined and represents an objective covariate. Future investigations are needed to validate the result of the present study.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

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