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Association of Pallidal Neurostimulation and Outcome Predictors With X-linked Dystonia Parkinsonism

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IMPORTANCE Anecdotal evidence suggests that deep brain stimulation (DBS) of the internal globus pallidus (GPi) is effective in ameliorating dystonia in X-linked dystonia parkinsonism (XDP), a disease that is usually refractive to medical therapy.

OBJECTIVE To determine the efficacy of GPi-DBS in a cohort of patients with XDP in a prospective study and identify predictors of postoperative outcomes.

DESIGN, SETTING, AND PARTICIPANTS This observational prospective cohort study enrolled patients in February 2013 and was completed in December 2014. The patients were followed up for up to 46 months. Patients from the Philippines were treated in a single center in Lübeck, Germany and followed up in the Philippines. Sixteen men with XDP (mean [SD] age, 40.9 [7.3] years; disease duration, 1-6 years) from the Philippines with predominant dystonia were selected.

EXPOSURES All patients underwent bilateral GPi-DBS in Lübeck, Germany.

MAIN OUTCOMES AND MEASURES Clinical assessment included the motor parts of the Burke-Fahn-Marsden scale (BFMDRS-M) and the Unified Parkinson's Disease Rating Scale (UPDRS-III). T1-based basal ganglia volumetry was performed and correlated with postoperative outcomes.

RESULTS The study participants included 16 Filipino men (mean age, 40.9 years). Masked video ratings revealed significant improvements of dystonia severity 1 week (−55%; range, −94% to 59%; $P < .01$) and 6 months (−59%; range, −100% to 22%; $P < .001$) after surgery. The UDPRS-III score also improved, albeit to a lesser extent (−19%; range, −54% to 95%; and −27%; range, −70% to 124%; respectively). Unmasked long-term follow-up confirmed the continued efficacy of GPi-DBS up to 46 months after surgery. Important secondary end points improved, including activities of daily living, pain severity, weight, and quality of life. Caudate atrophy was a predictor of a less beneficial outcome ($r = 0.817$, $P = .004$).

CONCLUSIONS AND RELEVANCE Internal globus pallidus DBS had a positive association in XDP with predominant dystonia (the primary end point) and contributed to an improved quality of life (the secondary end point). The response to DBS occurred within 1 week. Given the inverse correlation of postoperative benefit and caudate atrophy, GPi-DBS should be considered early during the disease course. Close international collaboration, training, and funding from multiple sources enabled the sustainable follow-up of patients with XDP in the Philippines.

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Video and Supplemental content

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X-linked dystonia parkinsonism (XDP) is a neurodegenerative movement disorder that affects mostly Filipino men owing to the X-linked recessive inheritance of a founder mutation in the TATA box-binding protein-associated factor 1 (*TAF1*) gene region.[1,2] X-linked dystonia parkinsonism is characterized by adult-onset focal or segmental dystonia, which rapidly generalizes within a few years. In most patients, dystonic symptoms become less severe and overlap or are replaced with parkinsonian features 5 to 10 years after disease onset.[3] Postmortem investigations identified a loss of striatal medium spiny neurons predominantly in the striosomal compartment, which resulted in striking striatal atrophy.[4-7]

Dystonia in XDP is severe and results in immobility, pain, insufficient food intake, weight loss, and aspiration, and oral treatments with antidystonic drugs are largely ineffective.[8] Deep brain stimulation of the internal pallidum (GPi-DBS) is an established therapeutic option in patients with treatment-refractory generalized and segmental-isolated dystonia[9] and has successfully been used in individual patients with XDP, providing anecdotal evidence only.[10,11] In this study, we prospectively determined the association of bilateral GPi DBS in 16 patients with XDP and combined clinical examinations with neuroimaging to identify predictors of postoperative outcome.

Key Points

Questions Is deep brain stimulation (DBS) an efficient therapeutic option in severe X-linked dystonia parkinsonism and what are predictors for the postoperative outcome?

Findings In this cohort study, pallidal DBS resulted in an improvement of dystonia and, to a lesser extent, parkinsonism. Deep brain stimulation was less effective in patients with more pronounced caudate atrophy.

Meaning Pallidal DBS should be considered a first-line treatment in medically intractable X-linked dystonia parkinsonism, and given the association of poorer treatment outcomes in patients with more advanced neurodegeneration, DBS should potentially be considered during the earlier stages of the disease.

Methods

Participants

From February 2013 to December 2014, 16 men from the Philippines (mean [SD] age, 40.9 [7.3] years; range, 30-52 years; mean [SD] disease duration, 3.2 [1.4] years; range, 1-6 years) with treatment-refractory XDP underwent GPi-DBS at the University Hospital Lübeck (eTable 1 and eMethods 1 in the Supplement). A multimodal research study accompanied the DBS procedure and was approved by the ethics committee of the University of Lübeck (AZ12-219). Before participation, informed written consent was obtained from all participants. Informed consent forms were translated to and explained in Tagalog, the official Filipino language.

Clinical Assessment

The primary outcome measure of this prospective study was the improvement of dystonia and parkinsonism after GPi-DBS. For dystonia, the motor part of the Burke-Fahn-Marsden scale (BFMDRS-M) was used, whereas parkinsonism was assessed with the Unified Parkinson's Disease Rating Scale part III (UPDRS-III). As tremor at rest is more common in parkinsonism than dystonia, a UPDRS-III subscore that focused on rest tremor as a cardinal parkinsonian sign was obtained to determine the response of a more specific parkinsonian feature to DBS (Rest Tremor Subscore [UPDRS-RT] = Sum of UPDRS-III Subitem 20). The distinction between parkinsonian rest tremors and dystonic tremors at rest is a clinical challenge in dystonia parkinsonism. Therefore, we analyzed 5 subitems of the 2 scales to gain insights into the changes of specific motor functions. Motor scores were analyzed by (1) a masked rating of standardized videos at 1 week and 6 months postsurgery by A.K. and J.V. and (2) an unmasked rating at the time of the clinical examination (on-site examination) for up to 46 months (eMethods 2 and 3 in the Supplement). Secondary end points included UPDRS-II scores, Schwab and England scores, global clinical impression scores (severity of illness: 1, normal; 7, among the most extremely ill patients), visual analog scale for pain scores, Hospital Anxiety and Depression Scale (HADS) scores, Montreal Cognitive Assessment (MoCA) scores, Frontal Assessment Battery (FAB) scores, Trail Making Test (TMT A and B) scores, and Short Form 36 (SF-36) scores. Basal ganglia volumetry was performed and the results were associated with the clinical variables (eMethods 4 in the Supplement).

Statistical Analysis

For the masked video rating, the means of the 2 observer-masked scores were compared at the preoperative, 1-week, and 6-month points using a 1-way analysis of covariance (ANOVA) with Tukey post hoc tests. Two videos were not available. A repeated-measures ANOVA was done for the scores that were obtained during the unmasked long-term follow-up examinations, taking into account 6 points. A Greenhouse-Geyser correction was applied in case that the sphericity had been violated using the Mauchly test. Subsequently, Tukey post hoc tests were performed and the mean of each column was compared with the mean of every other column. Secondary end points were compared using paired *t* tests; for HADS, MoCA, FAB, TMT A, TMT B, weight, and SF-36 domains, tests were done between the preoperative and postoperative periods between months 6 and 26. The statistical analysis for the remaining scores was carried out between preoperative and 6 months because the primary end point of motor improvement was assessed after 6 months. For categorial variables, χ^2 tests were performed. For correlations of behavioral data, the Pearson coefficient was calculated. For correlations of volumetric data, the relative volume of the basal ganglia in association with the total intracranial volume was used. Values of $<.05$ were considered significant except for analyses in which correction for multiple testing was done. When applicable, tests were done 2-sided. GraphPad Prism, version 7 (La Jolla) was used. Values are presented as mean (SD).

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Table. Data on Motor Signs, Daily Activities, Pain, and Global Disease Severity Before DBS and Different Postoperative Points From the Long-term Clinical Examinations

		Preoperative		1 wk		3 mo		6 mo		12 mo		Last Follow-up		
Scale	Score Range	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean Fellow-Up, mo
BFMDRS-M	0-120	58.1 (16.8)	16	29 (15.8)	16	16.1 (10.0)	16	27.1 (12.6)	14	19.3 (13.3)	12	27.2 (14.4)	15	33.9
UPDRS-III	0-108	38.9 (14.1)	16	28.5 (12.1)	16	16.5 (9.2)	14	17.2 (8.8)	16	12.8 (8.7)	11	21.7 (9.9)	13	33.6
UPDRS-II	0-52	20.4 (8.5)	16	NA	NA	10.3 (6.3)	14	9.9 (6.5)	16	12.0 (9.4)	11	12.8 (7.3)	11	27.7
Schwab England Disability Scale	0-100	61.3 (17.5)	16	NA	NA	NA	NA	85 (7.6)	8	94 (5.1)	10	74.4 (12.4)	9	27.1
Pain: VAS	0-10	5.2 (3.2)	13	3.1 (2.3)	11	2.2 (2.9)	11	2.2 (2.2)	13	3.2 (2.6)	9	2.3 (2.4)	11	26
Severity of illness, patient	1-7	4.9 (1.3)	13	2.5 (1.1)	11	2.1 (1.3)	9	2.3 (1.1)	11	2.1 (1.4)	10	NA	NA	NA
Severity of illness, caregiver	1-7	5.1 (1.5)	13	2.5 (0.9)	11	2.0 (1.2)	9	2.5 (1.1)	10	2.0 (1.2)	10	NA	NA	NA
Severity of illness, physician	1-7	5.2 (0.8)	14	2.3 (0.8)	14	2.0 (0.9)	8	2.2 (0.9)	10	1.8 (0.9)	10	NA	NA	NA

Abbreviations: BFMDRS-M, Burke-Fahn-Marsden scale; DBS, deep brain stimulation; NA, not applicable; UPDRS, Unified Parkinson's Disease Rating Scale.

Results

The preoperative BFMDRS-M score of 58.1 (SD, 16.8; range 33-88) indicated severe dystonia in the cohort (**Table**). The mean (SD) UPDRS-III score was 38.9 (14.1; range 18-59). Twelve patients had a dystonia-predominant phenotype (XDP-D) whereas 4 patients clearly had additional significant parkinsonism (XDP-DP).

Thirteen of the 16 operations (81.3%) were performed under general anesthesia because of excessive dystonic movements (eTable 1 in the Supplement). Nonrechargeable pulse generators were implanted (St. Jude Libra XP; electrode 6143; n = 10 [62.5%]; Medtronic Activa PC, electrode 3387; n = 6 [37.5%]).

Masked Video Ratings

Dystonia improved significantly following bilateral GPi-DBS ($F_{2,26}$ = 14.32; P < .001; n = 14 [87.5%]). The mean reduction on the BFMDRS scale was 55% at 1 week (range, −94% to 59%; P < .01) and 59% at 6 months (range, −100% to 22%; P < .001) after surgery (**Figure 1**, **Videos 1**, **2**, and **3**). There was a main association of DBS with the UPDRS-III score postoperatively ($F_{2,\ 26}$ = 4.51; P = .02). Post hoc tests for single points were significant at 6 weeks only (1 week, 19% reduction; P = .12; 6 months, 27% reduction; P = .002) (Figure 1B). There were no significant differences between observations at 1 week and 6 months, respectively (BFMDRS-M, P = .95; UPDRS-III, P = .65).

Long-term Follow-up Examination

The repeated-measures ANOVA revealed a significant reduction of the BFMDRS-M ($F_{5,45}$ = 27.3; P < .001) and a significant association with the UPDRS-III score ($F_{5,30}$ = 7.23; P = .015 [Greenhouse-Geyser corrected]) (Figure 1; Table). In regard to dystonia, the post hoc analysis showed significant differences between preoperative BFMDRS-M scores compared with any postoperative point. Significant differences were also observed when comparing BFMDRS scores 1 week postoperatively with those at 3 months, 3 months and last follow-up, and 6 months and last follow-up.

The post hoc analysis of the UPDRS-III demonstrated differences between preoperative scores compared with 3 months and 6 months and between 1 week and 6 months and 12 months postoperatively. The repeated-measures ANOVA revealed an association of DBS with the UPDRS-III-RT in the subgroup of 5 patients with XDP (31.3%) with a tremor at rest ($F_{2,30}$ = 3.55; P = .04) (Figure 1; **Video 3**). One patient (6.3%) (L-7673) developed parkinsonism following DBS (**Video 4**). An explorative analysis of single items of the UPDRS (items 29, 30, 31, and 18) and BFMDRS (item 3) revealed an improvement of gait (−54%; P < .001), postural instability (−84%; P < .001), bradykinesia and hypokinesia (−44%; P < .01), speech (−26%; P < .01), and speech and swallowing (−39%; P < .01) 6 months after the operation.

Secondary End Points

The UPDRS-II score had improved by 51% (n = 16 [100%]; P < .001), and the Schwab and England Disability Scale score by 39% (n = 8 [50%]; P < .01) (Table). Accordingly, most patients were less dependent than before surgery, and some patients regained employment. The scores for severity of illness significantly improved from the patients' (n = 11 [68.75%]; P < .001), caregivers' (n = 10 [62.5%]; P < .001), and physicians' perspective (n = 10 [62.5%]; P < .001). Pain visual analog scale scores decreased by 66% (n = 10 [62.5%]; P < .01). Depressive symptoms as assessed with the HADS score showed a trend toward improvement postoperatively (n = 12 [75%]; P = .05) whereas anxiety remained unchanged (n = 12 [75%]; P > .10) (eTable 2 in the Supplement). Four domains that were associated with quality of life (SF-36) improved after surgery (eTable 2 in the Supplement). Cognitive scores, including MoCA, FAB, and TMT A and B, remained unchanged after DBS.

Adverse events and stimulator settings are listed as eResults and the eTable 3 in the Supplement. Surgery-related adverse events occurred in 6 of 16 patients (37.5%) and included 2 asymptomatic intracerebral hemorrhages and 3 hematomas at the site of the pulse generator. All adverse events resolved without sequelae.

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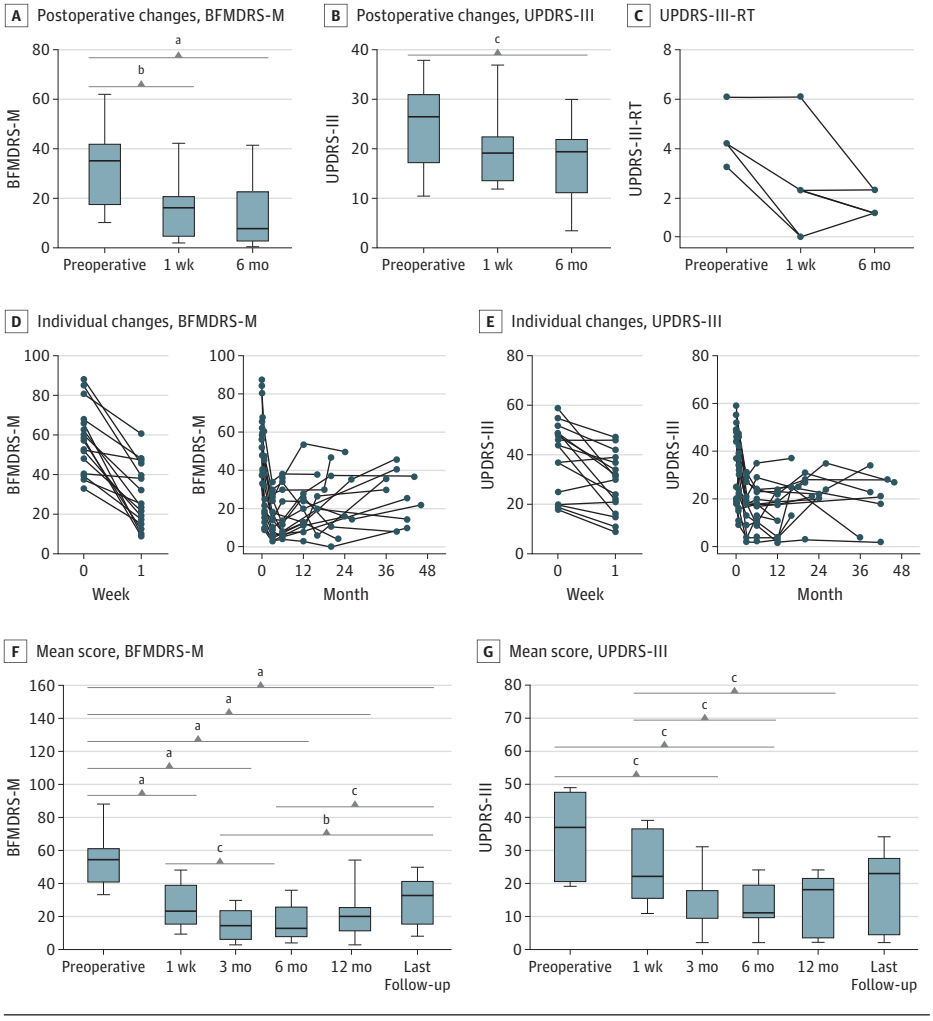
Figure 1. Primary End Points of Internal Global Pallidus Deep Brain Stimulation (GPi DBS) in 16 Men With X-linked Dystonia-Parkinsonism and Long-term Monitoring up to 46 Months Postoperatively



Postoperative changes of severity of dystonia and parkinsonism/general motor dysfunction as assessed by the Burke-Fahn-Marsden scale (BFMDRS-M) (A) and the Unified Parkinson's Disease Rating Scale (UPDRS-III) (B). For the primary end points, masked video ratings were used and the mean values were calculated across 2 independent raters (A.K. and J.V.). Dystonia severity improved by 55% at week 1 and by 59% 6 months postoperatively. The UPDRS-III score improved by 19% and 27%, respectively. Individual changes of the UPDRS-III resting tremor (RT) subscore (C) are shown, demonstrating that rest tremor as a cardinal sign of parkinsonism responded to DBS at the points 1 week and 6 months after surgery and indicating also that clear parkinsonian features respond to DBS. Individual changes of BFMDRS-M (D) and UPDRS-III (E) at 1 week, 3 months, 6 months, and 12 months after surgery and at the last follow-up (16-46 months postoperatively) in association with the clinical status before surgery in an unmasked manner. Mean BFMDRS-M (F) and UPDRS-III (G) scores of the unmasked evaluation are depicted. The whiskers in A, B, F, and G show minimum to maximum values, and the horizontal line in the boxes depict the mean. The boxes extend from the 25th to 75th percentiles.

[a] $P < .001$.

[b] $P < .01$.

[c] $P < .05$.

Basal Ganglia Volumetry

There was a high association between the volume of the caudate nucleus but not of the putamen or the globus pallidus with postoperative BFMDRS-M improvement 6 months after surgery ($r = 0.817$; $P = .004$), indicating that DBS was less effective in patients with a more pronounced caudate atrophy (**Figure 2**). No correlations were detected with regard to changes in the UPDRS-III score. There was also no association between caudate atrophy and preoperative dystonia severity (BFMDRS-M), severity of parkinsonism (UPDRS-III), and global cognitive function (MoCA) (P values between .17 and .97).

Discussion

To our knowledge, this is the first prospective and long-term follow-up study describing the efficacy and safety of GPi-DBS in patients with severe XDP and predominant dystonia. Deep brain stimulation led to a remarkable and long-lasting improvement of dystonia.[10,11] Notably, motor functions improved rapidly within a few days postoperatively, which was sustained during the follow-up period, such as in DYT1 dystonia.[12] In this regard, we observed a microlesion effect in some of the patients but stimulation had a clear additional association. Over the long-term course of the study, there was a slightly diminishing effect on the control of dystonia, which likely indicated disease progression given that the stimulation parameters were reviewed regularly and adjusted if necessary. As secondary outcome measures, disabling pain contributing to a reduced quality of life preoperatively was also markedly ameliorated and depressive symptoms showed a trend toward improvement. The improvement of quality of life of 67% on average across the different domains was at least comparable with most other studies in which improvement was 50% at the most.[13] Unlike potential deterioration in patients with Parkinson disease undergoing subthalamic nucleus DBS, global cognitive functions were unchanged after GPi-DBS in our sample, which is an important safety measure. The observed bleeding complications, including 2 small asymptomatic intracerebral hemorrhages, resolved without sequelae. The reasons are speculative but the preoperative nutritional status and disease-related effects may have contributed to these adverse

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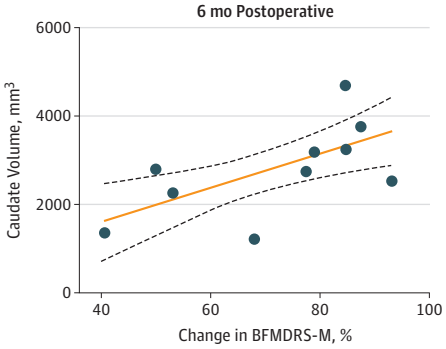
events. In the previously published case reports, intracranial hemorrhage was not mentioned as a frequent adverse event; therefore, this complication may just have incidentally occurred in the patients in this study.

Atrophy of the caudate nucleus was associated with a less beneficial response of motor symptoms to DBS, which indicated that this surgical intervention may be more favorable when neurodegeneration is less advanced. Caudate atrophy was not associated with preoperative disease severity, which argues for a specific interaction of atrophy and the ability of DBS to alleviate dystonic symptoms. In other types of dystonias, no such structural surrogate markers have been identified as most forms of dystonia are not accompanied by neurodegenerative changes. However, several studies indicate that early DBS in severe dystonia is a predictor for a beneficial postoperative outcome.[12,14,15]

Limitations

The variability of response to DBS was considerably higher for the UPDRS-III score compared with the BFMDRS-M score, in keeping with the notion that the assessment of parkinsonism in a combined dystonia parkinsonism syndrome poses a major clinical challenge. In response to this, recently a dedicated rating scale was developed and validated in 204 patients with XDP, but it was not yet available for this study.[16] Because nonrechargeable DBS batteries were implanted initially, it was expected that the symptomatic effect of neurostimulation would last for a limited time only. In anticipation of this problem, we applied for further funding, allowing for subsequent battery replacement.

Figure 2. Caudate Volume



Caudate volume correlated negatively with the degree of improvement of dystonias as assessed with the Burke-Fahn-Marsden scale (BFMDRS) (r = 0.817, P = .004). The dotted lines indicate 95% CIs.

Conclusions

Internal global pallidus DBS should be considered as a first-line treatment in medically intractable XDP. Because advanced neurodegeneration was associated with a poorer response, DBS should be considered during the early stages of the disease. Close collaboration, trust-based relationships, continuous education, and multiple-source funding (eDiscussion in the Supplement) were mainstays of success for the project, which may serve as a model from which to embark on complex clinical interventions in resource-challenged settings.

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Author Contributions: Dr Brüggemann had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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