RESEARCH ARTICLE

Quality of Life After Deep Brain Stimulation of Pediatric Patients with Dyskinetic Cerebral Palsy: A Prospective, Single-Arm, Multicenter Study with a Subsequent Randomized Double-Blind Crossover (STIM-CP)

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ABSTRACT: Background: Patients with dyskinetic cerebral palsy are often severely impaired with limited treatment options. The effects of deep brain stimulation (DBS) are less pronounced than those in inherited dystonia but can be associated with favorable quality of life outcomes even in patients without changes in dystonia severity.
Objective: The aim is to assess DBS effects in pediatric patients with pharmacorefractory dyskinetic cerebral palsy with focus on quality of life.
Methods: The method used is a prospective, single-arm, multicenter study. The primary endpoint is improvement in quality of life (CPCHILD [Caregiver Priorities & Child Health Index of Life with Disabilities]) from baseline to 12 months under therapeutic stimulation. The main key secondary outcomes are changes in Burke-Fahn-Marsden Dystonia Rating Scale, Dyskinesia Impairment Scale, Gross Motor Function Measure-66, Canadian Occupational Performance Measure (COPM), and Short-Form (SF)-36. After 12 months, patients were randomly assigned to a blinded crossover to receive active or sham stimulation for 24 hours each. Severity of dystonia and chorea were blindly rated. Safety was assessed throughout. The trial was registered at ClinicalTrials.gov, number NCT02097693.
Results: Sixteen patients (age: 13.4 $\pm$ 2.9 years) were recruited by seven clinical sites. Primary outcome at 12-month follow-up is as follows: mean CPCHILD increased by 4.2 $\pm$ 10.4 points (95% CI [confidence interval] −1.3 to 9.7; $P = 0.125$); among secondary outcomes: improvement in COPM performance measure of 1.1 $\pm$ 1.5 points (95% CI 0.2 to 1.9; $P = 0.02$) and in the SF-36 physical health component by 5.1 $\pm$ 6.2 points (95% CI 0.7 to 9.6; $P = 0.028$). Otherwise, there are no significant changes.
Conclusion: Evidence to recommend DBS as routine treatment to improve quality of life in pediatric patients with dyskinetic cerebral palsy is not yet sufficient. Extended follow-up in larger cohorts will determine the impact of DBS further to guide treatment decisions in these often severely disabled patients.

Key Words: children; deep brain stimulation; dyskinetic cerebral palsy; prospective trial; quality of life

Cerebral palsy (CP) includes a heterogeneous group of developmental disorders due to nonprogressive disturbances that occur in the developing fetal or infant brain, with a prevalence of 17 to 31 per 1000 live births.[1] Some patients (10%–15%) present with dystonia and/or choreo-athetosis as the major movement disorder pattern and are diagnosed as dyskinetic CP (DCP).[2] Most patients with DCP are severely physically disabled due to abnormal movements and posturing and consequent musculoskeletal deformities. Motor impairments are often accompanied by nonmotor comorbidities such as disturbances in cognition, communication, nutritional intake, and sleep.[2]

Management of DCP is particularly challenging because pharmacological treatment is often ineffective or limited by medication-related side effects.[3] Deep brain stimulation of the globus pallidus internus (GPi-DBS) has proven to be an effective and safe treatment option for patients with pharmacorefractory inherited, isolated generalized, or segmental dystonia.[4] Results of retrospective case series and one prospective trial with 13 adult DCP patients also report beneficial effects, assessed using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS).[5–7] However, these effects were far less pronounced and more variable compared to patients with inherited dystonia. Yet even in DCP patients with little or absent observable changes in the BFMDRS, DBS can improve domains such as function and quality of life, suggesting that the BFMDRS alone does not capture all aspects of the clinical picture in these patients.[8]

Our prospective study investigated the impact of GPi-DBS on motor and nonmotor domains, with a special focus on quality of life in a cohort of exclusively pediatric DCP patients. We aimed to improve the counseling of patients and their families regarding the treatment effects and outcome prognosis with GPi-DBS and to refine the patient selection process for DBS.

Patients and Methods

Study Design

STIM-CP is a multicenter, single-arm, pre-post trial using a within-patient control to document patient outcomes for bilateral GPi-DBS in the treatment of DCP for 12 months.[9]

After assessment of primary and secondary outcome parameters under continuous therapeutic stimulation for 12 months, an additional randomized, double-blind, crossover phase was implemented to detect immediate, even subtle stimulation effects on dystonia and choreo-athetosis that might have been missed during the initial 12-month follow-up (Fig. 1).[9] The trial conformed to the Helsinki Declaration and Good Clinical Practice Guidelines and was approved by the ethics committees of Cologne on January 31, 2014 (13-359; trial protocol code Uni-Koeln 1603), and by each of the participating centers. All capable patients or their legal caregivers provided written informed consent. Beyond 12 months, further follow-up visits at 24 and 36 months were planned but do not form part of this article.

Source data verification, data management, serious adverse events (SAEs), and project management were performed by the Clinical Trials Centre Cologne, Germany. The trial conduct and safety of the participants were overseen by the Data Monitoring Committee, which periodically assessed adverse events (AEs) and monitored the integrity and validity of the collected data.

The study was registered at ClinicalTrials.gov (NCT02097693).

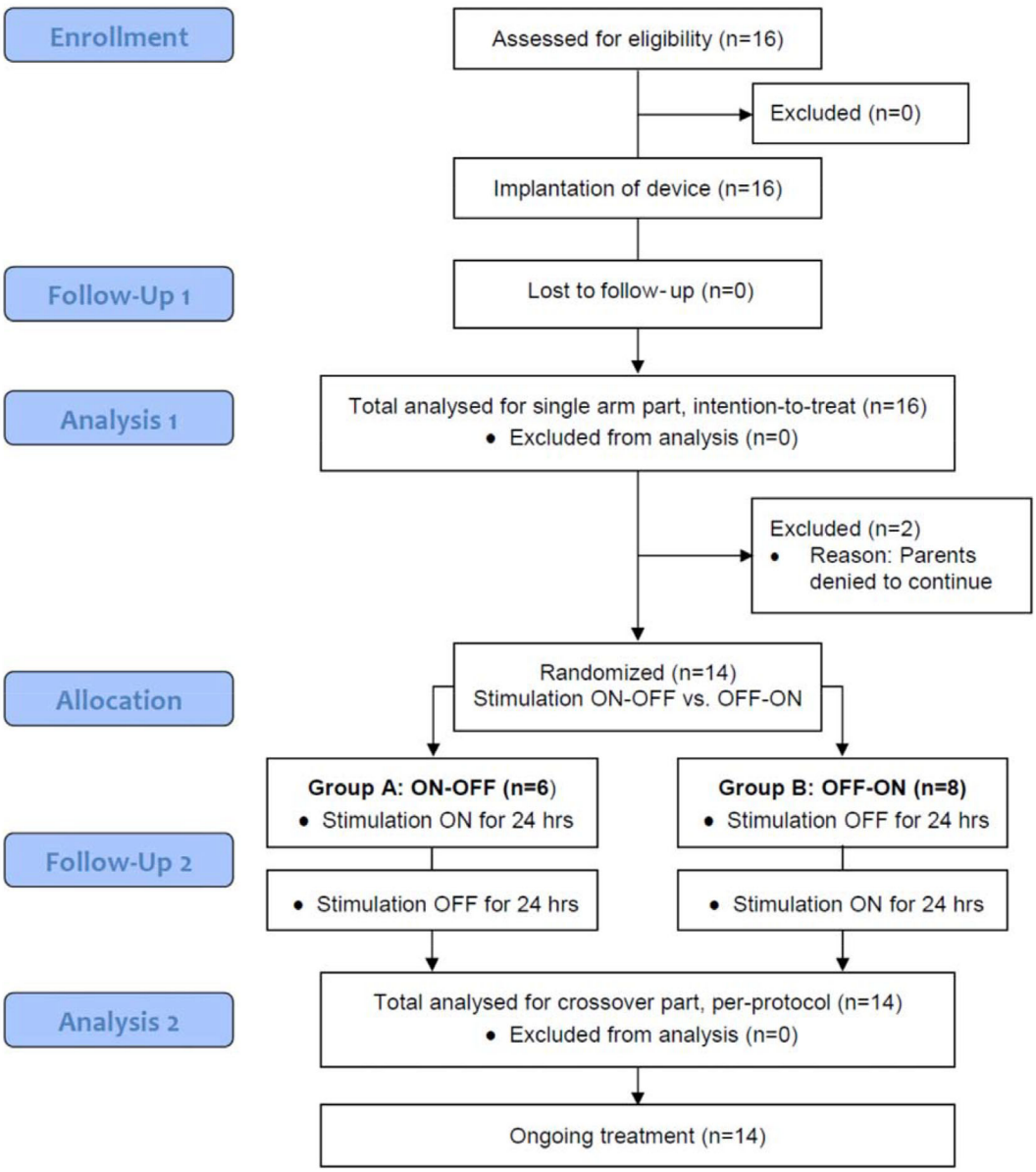

FIG. 1. CONSORT 2010 flow diagram. [Color figure can be viewed at wileyonlinelibrary.com]

Participants

We recruited pediatric patients who were aged between 7 and 18 years and diagnosed with DCP. Patients were eligible if they met the following main inclusion criteria: acquired dystonia due to perinatal hypoxic brain injury, GPi-DBS chosen for treatment, posteroventral lateral GPi, and motor thalamus mostly intact on latest magnetic resonance imaging (MRI) scan. The main exclusion criteria were inherited (genetic) or idiopathic dystonia, severe axial hypotonia with total loss of head control (eg, absence of control at the "upper thoracic level" in the Segmental Assessment of Trunk Control, medication effect excluded), fixed hemi-dystonia, severe spasticity in knee and elbow flexors and extensors (Modified Ashworth Scale >3 for each segment), fixed severe skeletal deformations with the loss of function requiring immediate orthopedic surgical intervention, and other severe concurrent neurological disease.

Procedures

Seven visits were scheduled. Eligible patients were included at the screening visit. A comprehensive preoperative assessment including all primary and secondary outcome parameters was performed at the baseline visit (V0), 0-6 weeks before implantation. At implantation visit (V1), all patients underwent simultaneous bilateral stereotactic implantation of electrodes into the posteroventral lateral GPi, which were connected to an implantable pulse generator (Vercise or Vercise Gevia DBS System, Boston Scientific, Valencia, CA, USA). DBS implantation was not part of the study protocol and was performed according to the institutional protocols of each center.

For initial programming, the threshold for unwanted side effects (eg, phosphenes, muscle contractions, paresthesia, and dysarthria) was tested by monopolar review for each contact at a frequency between 90 and 130 Hz and a pulse width between 90 and 150 μs. The therapeutic contacts were finally selected if there were no or only late AEs under the highest stimulation intensity, and a possible reduction in dystonia. The amplitude was set at a minimum of 0.2 mA below the threshold for side effects, and active stimulation was started within the first week after implantation. All patients received continuous therapeutic stimulation during 12 months of follow-up. A target for effective stimulation was set at approximately 6 months after implantation. In the case of directional leads, directional stimulation was avoided if possible to increase comparability with patients implanted with nondirectional leads.

Primary and secondary outcome parameters were assessed during follow-up visits at 3, 6, 9, and 12 months after implantation (V2-5) under therapeutic stimulation by the participating sites (Table APPENDIX S1).

Randomization and Blinding

After 12 months (V5), patients were randomly assigned (1:1) using sequentially numbered sealed opaque envelopes that were produced based on a computer-generated randomization list (blocked randomization stratified by site). Patients received either active followed by sham (amplitude: 0 mA) stimulation (group A) or sham followed by active stimulation (group B); each stimulation mode was applied for 24 hours (Fig. 1). A study nurse opened the envelopes, assigned the participants to the trial groups, and changed the stimulation settings accordingly. Patients and treating physicians were blinded for stimulation settings.

Standardized videos were taken at baseline, 12 months, and during crossover (after 24 and 48 hours, at the end of each stimulation phase) according to a protocol for the BFMDRS movement score (BFMDRS-M) and Dyskinesia Impairment Scale (DIS). To ensure comfort and safety of the pediatric patients, the duration of the crossover was limited to only 24 hours for each phase as we did not want to withhold treatment to patients with good response for a longer period.

Primary and Secondary Outcomes

To focus on patient-related outcome measures, the mean change in the Caregiver Priorities & Child Health Index of Life with Disabilities (CPCHILD) questionnaire, developed to measure caregivers' perspectives on health status, comfort, well-being, functional abilities, and ease of caregiving of nonambulatory children with CP aged 5 to 18 years, from baseline to 12 months (V5) after first lead implantation, was chosen as the primary endpoint.[10] As a hypothesis, we expected at least a 10-point increase in the total standardized score of the CPCHILD from preoperative to 12 months under continuous active stimulation.

Key secondary outcomes were changes in CPCHILD at V3; BFMDRS movement (BFMDRS-M) and disability scores (BFMDRS-D), DIS, Short-Form (SF)-36 of patients and caregivers, Family Burden (FaBel), Wong Baker Faces, Frenchay Dysarthria Assessment (FDA), and Clinical Global Impression (CGI) at V3 and V5; Gross Motor Function Measure-66 (GMFM-66), Canadian Occupational Performance Measure (COPM), and Strength and Difficulties Questionnaire (SDQ) at V5 (Table APPENDIX S1).

The BFMDRS-M and DIS total at baseline (V0), 12-month visit (V5), and during randomization were rated by masked experts for movement disorders without any details regarding group or visit date (BFMDRS-M: W.M., A.P.; DIS: E.M.).

The monitoring of (severe) AEs started on the day of implantation and ended 4 weeks after final assessment.

Statistical Analysis

A sample size of 16 patients would provide 85% power with a two-sided significance level of $\alpha = 0.05$ to detect a clinically relevant change (preoperative to 12 months after the first lead implantation) in CPCHILD of 10 points, assuming a normally distributed difference with a standard deviation of 12.6.[10,11] Similarly, for the randomized crossover comparison 8 patients per group (ON–OFF vs. OFF–ON) are sufficient to detect a standardized mean difference of 0.8 (effect size Cohen's d) with a power of 0.85 (at two-sided significance level 0.05, paired *t* test).

To account for up to 20% attrition, recruitment of 20 patients was intended.

The statistical methods applied included contingency table analysis, descriptive methods, and linear mixed models. Continuous variables were summarized by valid n and mean ± standard deviation, categorical variables by counts, and percentages. Confidence intervals (CI, 95% level) were calculated where appropriate.

Analysis of the pre–post comparison included all enrolled patients (intention-to-treat [ITT] approach). The change in the primary variable CPCHILD (total standardized score) from preoperative to 12 months after the first lead implantation was analyzed by a paired *t* test (two sided). The primary analysis of the crossover part comprised all randomized patients who were treated and observed per protocol (PP). The two-period crossover data were analyzed using the Hills–Armitage approach.[12] Statistical analyses were performed using the software SPSS 26 Statistics (IBM Corp., Armonk, NY, USA).

Results

Sixteen patients (ITT population) were recruited by seven clinical sites between February 28, 2014, and April 4, 2019. The mean age was 13.4 ± 2.9 (range: 8–18) years (6 girls). Table 1 presents the baseline characteristics of the patients enrolled in the study. After bilateral electrode implantation in the GPi, patients were followed up at implantation and at 3-, 6-, 9-, and 12-month visits. Precise electrode localization was confirmed by postoperative CT (computed tomography) fused with preoperative MRI in accordance with clinical routine (Fig. APPENDIX S1).

The mean stimulation parameters were amplitude, 2.5 ± 1.2 mA; pulse width, 108 ± 49 μs; and frequency, 117 ± 26 Hz at 12 months.

At baseline, 10 patients took medication for their movement disorder, including benzodiazepines (n = 3 patients), anticholinergic drugs (3), baclofen (1), cannabinoids (1), dopamine antagonists (2), dopamine agonists (3), and nonopioid analgesics (1). Four patients received

TABLE 1 *Baseline characteristics in patients included in the single-part analysis (intention to treat)*

Characteristics	Patients in single-arm part (n = 16)
Age at inclusion (median, interquartile range)	14.0 (12.0 to 15.5)
Sex	
Male	10
Female	6
Diagnosis	
Acquired dystonia due to perinatal hypoxia	16
Birth	
Term	9
Preterm	6
Extreme preterm (<32 weeks of gestation)	1
Dystonia	
Isolated	0
Combined	16
Choreo-athetosis	
Yes	12
No	4
Truncal hypotonia	
Yes	5
No	11
Spasticity in lower and/or upper extremity[a,b]	
Yes	6
No	9
GMFCS level[a]	
III	1
IV	5
V	9
Cranial MRI abnormalities	
Yes[c]	14
No	2
Anti-dystonic medication	
Yes	10
No	6

Abbreviation: MRI, magnetic resonance imaging.
[a]Missing data for patients (n = 1 spasticity, n = 1 GMFCS level).
[b]Modified Ashworth Scale ≤3. Data are numbers, unless otherwise stated. GMFCS, Gross Motor Function Classification System.
[c]n = 11 patients with lesions affecting parts of the basal ganglia and/or thalamus to varying extents.

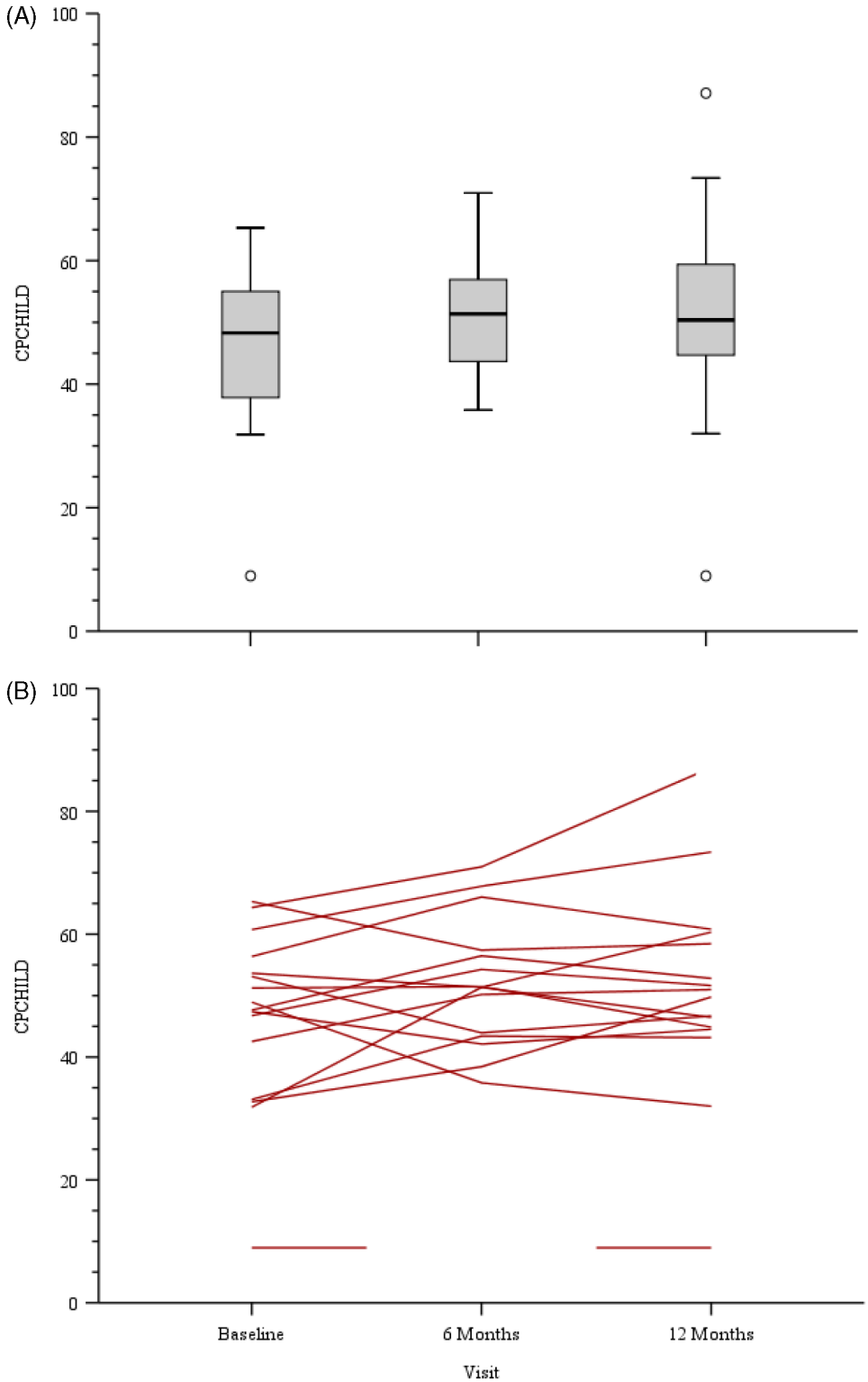

FIG. 2. CPCHILD scale before surgery (baseline) and 6 and 12 months after surgery. Legend: Boxplots represent (**A**) mean, 25th and 75th percentile, and the whiskers 95th percentile; (**B**) individual courses. CPCHILD, Caregiver Priorities & Child Health Index of Life with Disabilities. [Color figure can be viewed at wileyonlinelibrary.com]

botulinum toxin A injections. At 12 months, the number of medications increased in 1 patient (benzodiazepine added) but was unchanged in the remaining patients.

Two patients withdrew their consent for randomization because the families declined to continue, leaving 14 patients randomized to crossover (PP population):

TABLE 2 *Primary and key secondary outcomes before surgery (baseline) and 6 and 12 months after surgery (intention to treat)*

Scales		Baseline	6 months	Difference	Percentage change	*P*-value[a]	12 months	Difference	Percentage change	*P*-value[a]
CPCHILD	Valid n	16	15	15	15		16	16	16	
	Mean (SD)	46.5 (14.4)	52.1 (10.5)	3.0 (8.9)	8.7 (21.8)	0.211	50.7 (17.0)	4.2 (10.4)	10.7 (23.2)	0.125
	Median	48.3	51.4	6.6	11.6		50.4	5.0	10.7	
	95% CI	(38.9 to 54.2)	(46.2 to 57.9)	(−1.9 to 8.0)	(−3.4 to 20.8)		(41.7 to 59.8)	(−1.3 to 9.7)	(−1.7 to 23.0)	
BFMDRS Movement score (blinded)	Valid n	15					14	14	14	
	Mean (SD)	80.3 (21.6)					80.7 (23.1)	0.1 (5.2)	0.0 (7.0)	0.960
	Median	77.5					82.0	0.3	0.4	
	95% CI	(68.4 to 92.3)					(67.4 to 94.0)	(−2.9 to 3.1)	(−4.1 to 4.0)	
BFMDRS Disability score (binded)	Valid n	16	16	16	16		15	15	15	
	Mean (SD)	25.0 (4.5)	24.8 (4.4)	−0.3 (1.1)	−0.6 (5.0)	0.388	24.8 (4.7)	−0.3 (1.4)	−0.7 (6.2)	0.484
	Median	26.0	25.5	0.0	0.0		26	0.0	0.0	
	95% CI	(22.6 to 27.4)	(−18.0 to 9.5)	(−0.8 to 0.3)	(−3.3 to 2.0)		(22.2 to 27.4)	(−1.1 to 0.5)	(−4.1 to 2.7)	
DIS Dystonia (blinded)	Valid n	14					14	14	14	
	Mean (SD)	122.5 (38.1)					133.9 (36.2)	10.4 (29.1)	5.4 (21.2)	0.206
	Median	136					132	−0.5	2.7	
	95% CI	(101.3 to 143.6)					(113.9 to 154.9)	(−6.4 to 27.2)	(−6.8 to 17.7)	
DIS Choreo-athetosis (blinded)	Valid n	15					15	14	14	
	Mean (SD)	67.1 (32.9)					65.3 (27.2)	−3.4 (18.3)	0.4 (22.7)	0.495
	Median	63					68	0.5	1.2	
	95% CI	(48.9–85.3)					(50.2 to 80.3)	(−14.0 to 7.1)	(−12.7 to 13.5)	
DIS Total score (blinded)	Valid n	15					15	14	14	
	Mean (SD)	189.6 (51.3)					199.2 (50.7)	6.9 (33.4)	14.6 (38.8)	0.452
	Median	188.0					200.0	5.0	−0.01	
	95% CI	(162.2 to 218.0)					(171.1 to 227.3)	(−12.4 to 26.2)	(−7.8 to 37.0)	
COPM, performance	Valid n	14					14	14	14	
	Mean (SD)	2.8 (1.5)					3.9 (2.2)	1.1 (1.5)	64.0 (117.8)	0.020★
	Median	2.9					3.8	0.8	33.3	
	95% CI	(2.0 to 3.7)					(2.6 to 5.1)	(0.2 to 1.9)	(−4.0 to 132.0)	

(Continues)

TABLE 2 *Continued*

Scales		Baseline	6 months	Difference	Percentage change	*P*-value[a]	12 months	Difference	Percentage change	*P*-value[a]
COPM, satisfaction	Valid n	14					14	14	14	
	Mean (SD)	2.9 (1.4)					3.7 (2.2)	0.7 (1.4)	25.9 (55.5)	0.730
	Median	2.9					3.6	0.2	11.3	
	95% CI	(2.1 to 3.7)					(2.4 to 5.0)	(−0.1 to 1.6)	(−6.1 to 57.9)	
SF-36 Physical health (patient)	Valid n	10	10	10	10		10	10	10	
	Mean (SD)	32.3 (6.7)	31.8 (6.9)	−0.5 (7.6)	1.3 (24.3)	0.844	37.5 (8.1)	5.1 (6.2)	17.1 (17.7)	0.028★
	Median	33.6	31.5	2.0	7.2		38.2	6.2	22.3	
	95% CI	(27.6 to 37.1)	(26.9 to 36.8)	(−5.9 to 5.0)	(−16.1 to 18.7)		(31.6 to 43.3)	(0.7 to 9.6)	(4.4 to 29.8)	
SF-36 Mental health (patients)	Valid n	10	10	10	10		10	10	10	
	Mean (SD)	56.3 (10.0)	53.2 (11.1)	−3.1 (16.1)	−1.8 (29.8)	0.557	56.5 (10.3)	0.2 (12.4)	3.1 (28.2)	0.970
	Median	59.1	56.9	−0.4	−0.3		59.4	−1.1	−1.7	
	95% CI	(49.2 to 63.5)	(45.3 to 61.2)	(−14.6 to 8.4)	(−23.2 to 19.5)		(49.1 to 63.8)	(−8.7 to 9.0)	(−17.1 to 23.2)	
SF-36 Physical health (carer)	Valid n	15	15	15	15		15	15	15	
	Mean (SD)	40.0 (13.3)	44.9 (13.4)	4.9 (7.4)	20.8 (40.6)	0.022	44.8 (14.2)	4.6 (7.3)	17.1 (34.8)	0.029★
	Median	44.8	47.4	5.0	9.4		50.3	3.3	9.2	
GMFM-66	95% CI	(32.6 to 47.3)	(37.5 to 52.3)	(0.8 to 9.1)	(−1.7 to 43.3)		(37.2 to 52.4)	(0.5 to 8.6)	(−2.2 to 36.4)	
	Valid n	16					15	15	15	
	Mean (SD)	18.4 (18.1)					19.0 (20.2)	1.7 (3.2)	15.5 (38.5)	0.052
	Median	8.8					8.5	1.6	5.4	
	95% CI	(8.7 to 28.0)					(7.73 to 0.2)	(−3.8 to 0.02)	(−5.8 to 36.8)	

[a]Paired *t* test.

★Statistically significant if $P < 0.05$. Data are valid n, mean (standard deviation [SD]), median, and 95% confidence interval (CI).

Abbreviations: CPCHILD, Caregiver Priorities & Child Health Index of Life with Disabilities; BFMDRS, Burke-Fahn-Marsden Dystonia Rating Scale; DIS, Dyskinesia Impairment Scale; COPM, Canadian Occupational Performance Measure; SF-36, Short Form-36; GMFM-66, Gross Motor Function Measure-66.

TABLE 3 *Adverse events (AEs) and serious adverse events (SAEs) by relatedness and with outcome during the initial 12-month follow-up*

	Recovered without sequelae	Not yet recovered
SAEs (possibly) related to surgery, device and/or stimulation	**4**	**0**
Febrile seizure	1	0
Fever	1	0
Implant site infection	1	0
Intracerebral hemorrhage	1	0
AEs (possibly) related to surgery, device and/or stimulation	**10**	**1**
Device use error*	2	0
Dyskinesia or dyskinesia aggravated	1	1**
Inappropriate device programming*	1	0
Fatigue	1	0
Headache	2	0
Hypersalivation	1	0
Scar pain	1	0
Seroma	1	0
SAEs not related to surgery, device and/or stimulation	**2**	**0**
Benzodiazepine intoxication	1	0
Rhonchopathy	1	0
AEs not related to surgery, device and/or stimulation	**15**	**1**
Blistering	1	0
Dystonia aggravated	1	0
Fall	1	0
Fungal infection	1	0
Pain aggravated	1	0
Nose injury	1	0
Reduced general condition	1	0
Shoulder dislocation	0	1
Infection respiratory	8	0
All SAEs and AEs	**31**	2
Related to surgery, device and/or stimulation	14	1**
Not related to surgery, device and/or stimulation	17	1

*leading to increase of dystonia or dyskinesia; **restored beyond 12-months follow-up.

group A (stimulation ON–OFF), n = 6; group B (stimulation OFF–ON), n = 8 (Fig. 1).

Primary Outcome

After 12 months of continuous stimulation, the change in the mean standardized CPCHILD score was 4.2 ± 10.4 (95% CI −1.3 to 9.7) points (46.5 ± 14.4 at baseline vs. 50.7 ± 17.0 at 12 months; $P = 0.125$) without reaching statistical significance. The increase was ≥10 points in 5 of 16 patients and >10% from baseline in 9 patients (Fig. 2). CPCHILD subitems did not change significantly (Table S2).

Distinguishing between the two groups of term-born (≥37 weeks of gestation) and preterm-born patients (<37 weeks of gestation), the mean change in CPCHILD from baseline to 12-month follow-up in the group of preterm-born was 9.03 ± 9.17 ($P = 0.04$) versus 0.46 ± 10.11 ($P = 0.895$) in the group of term-born patients.

Secondary Outcomes

The COPM performance score improved from baseline to 12 months (change 1.1 ± 1.5 [95% CI 0.2 to 1.9] points; $P = 0.02$), without any significant change in the COPM satisfaction score. Patients and caregivers also indicated improvement in the SF-36 physical health component (patients, change 5.1 ± 6.2 [95% CI 0.7 to 9.6] points; $P = 0.028$; caregivers, change 4.6 ± 7.3 [95% CI 0.5 to 8.6] points; $P = 0.029$). The mean change in the GMFM-66 was 1.7 ± 3.2 (95% CI 0 to 3.5) points; $P = 0.052$ (Fig. S2). After 12 months, there were no significant changes in the BFMDRS nor in the DIS, including subscores (Table 2; Tables S3a and b).

Further analyses revealed a strong inverse correlation between the baseline scores of BFMDRS-M and GMFM-66 (correlation coefficient: −0.821, $P < 0.0001$).

After 12 months, physician-rated CGI of dystonia severity was rated "much improved" in 10 of 14 patients, "minimally improved" in 2 of 14 patients, and "no change" or "minimally worse" in 2 of 14 patients compared to baseline (Table S4). There were no significant changes in the scores for Wong Baker Faces for pain perception (change −0.14 ± 2.14 [95% CI −1.38 to 1.09] points; $P = 0.807$), the FaBel (change 0.16 ± 2.36 [95% CI −1.20 to 1.52] points; $P = 0.803$), the SDQ (externally assessed by parents; change 0.9 ± 5.8 [95% CI −3.9 to 5.7] points; $P = 0.681$), and the FDA (change −2.6 ± 5.8 [95% CI −6.3 to 1.1] points; $P = 0.681$).

Randomized Crossover

After randomization, the secondary outcome parameters DIS and BFMDRS were compared for active and sham stimulation, each provided for 24 hours. No significant difference between the stimulation modes (ON–OFF) was found with regard to BFMDRS-M

(mean difference derived from Hills–Armitage approach 4.11 points [95% CI –1.59 to 9.92]; $P = 0.141$) or to DIS (DIS total mean difference −5.9 points [95% CI –25.00 to 13.26]; $P = 0.513$) (Table S5).

Adverse Events

During the 12-month follow-up, 33 AEs were reported in 10 of 16 patients (Table 3). Of these, 6 SAEs occurred in 4 of 16 patients and 27 nonserious AEs in 6 of 16 patients. All events classified as related, possibly related, or not assignable were categorized as related. Overall, 15 events were treatment related. Four SAEs were related or possibly related to treatment. In 1 patient, a small asymptomatic cortical cerebral hemorrhage was detected on postoperative CT, 1 patient had a tissue infection by methicillin-resistant *Staphylococcus aureus* around the burr hole, and 2 patients were admitted to hospital, one due to a febrile seizure and the other for fever of unknown origin. All (possible) treatment-related serious and nonserious AEs fully resolved, apart from one AE that resolved only after the 12-month follow-up (Table S5).

Discussion

To our knowledge, this is the first prospective trial investigating the effects of GPi-DBS in pediatric DCP patients. After 12 months of chronic DBS treatment, the primary outcome, change in quality of life assessed by the CPCHILD, increased, but significance could not be reached. Distinguishing between term- and preterm-born patients, there was a trend toward improvement in quality of life in the group of preterms. Due to small numbers in these subgroups, the data have to be interpreted with caution, and further investigation is needed to explore whether the week of gestation correlates with outcome. Among the secondary parameters, GPi-DBS significantly improved the performance of individual activities of daily living and physical health-related quality of life in patients and caregivers. No other secondary outcomes changed significantly during follow-up or randomized crossover.

There was an overall variability in all motor- and nonmotor outcomes investigated. This is in accordance with previously published data reporting that DBS effects in patients with acquired dystonia are less pronounced and more heterogeneous than in patients with inherited, isolated dystonia.[5–7] Although this cohort was highly selected, the patients' clinical phenotype, often comprising a complex motor disorder with hyper- and hypokinetic components, spasticity, truncal hypotonia, and joint contractures, and the level of impairment were still heterogeneous. Even if DBS alleviated dystonia, the remaining concomitant symptoms may still lead to severe impairment, limiting the overall effect on motor function.[13]

The etiology may also account for differences in response. The most common cause of DCP is perinatal asphyxia, which causes neuronal damage in multiple brain regions within the motor network. In particular, the basal ganglia and thalamus are most vulnerable to perinatal hypoxia due to high metabolic demand toward the end of pregnancy.[14] Dystonia is a network disorder with inputs from different brain areas, such as the cerebellum, brainstem, sensorimotor cortex, and various parallel or segregated circuits within the cortex–basal ganglia–thalamus loops.[15] Depending on the pattern of injury within this network, DCP patient phenotype can be heterogeneous. DBS stimulates neural tissue around the implanted electrodes and can modulate certain neuronal circuits but cannot compensate for structural lesions in distant parts of the brain. It is of note that 4 of 5 patients with ≥10-point improvement in the CPCHILD were not reported to have thalamic lesions (Table S5). Therefore, whether the pattern of structural lesions may be an outcome predictor needs to be further explored. In addition, clinical neurophysiological parameters provide information on the integrity of sensory and motor pathways and the impact of structural lesions. Previous retrospective data suggested a correlation between abnormal preoperative central motor conduction time and somatosensory-evoked potentials and poor DBS outcome in a cohort of patients with dystonia.[16] Therefore, these parameters may contribute further as predictive markers of DBS outcome and could be included in the multimodal assessment of potential candidates for DBS.

Dystonia severity may also influence outcome. One larger prospective DBS trial in adults with DCP reported a mean BFMDRS improvement of 24.4%.[6] Despite similar inclusion criteria, all our patients were classified as "nonresponders" due to <20% improvement in the postoperative BFMDRS. Previous data suggested a negative correlation between preoperative BFMDRS and percentage postoperative improvements in DCP patients.[5] This is comparable to our cohort, which included patients more severely affected by dystonia compared to the referred cohort (BFMDRS-M 80.3 vs. 44.2 points, respectively[6]).

Furthermore, DCP patients manifest dystonia during early infancy. Unlike most patients with inherited dystonia, these patients are not able to learn normal motor milestones during early development. Therefore, it is not clear to what extent DBS enables the development of purposeful motor skills.[17] In Lumsden and colleagues, DBS outcomes correlated with the proportion of life lived with dystonia.[18] One might speculate that patients without normal motor patterns during their life span because of perinatal brain damage could slowly learn effective movements but do not benefit from the

potential to "flip back" into a previously acquired healthy motor reserve.[18] Therefore, there is an unmet need to implement systematic therapeutic, habilitation, or rehabilitation strategies for these patients.[19]

Differences in assessment approaches may also account for variations in outcome. The indication for DBS in this cohort was dystonia, which is most often assessed by the BFMDRS. However, the BFMDRS was initially developed for adults with isolated dystonia.[20] In DCP patients, dystonia is not the only disabling feature. Fluctuation in tone, presence of other movement disorders, and/or orthopedic deformities make it difficult to quantify dystonia and identify changes thereof.

In terms of gross motor function, the change in GMFM-66 narrowly failed to achieve statistical significance, whereas there was a strong inverse correlation between the baseline GMFM-66 and the BFMDRS. This could be attributed to potential floor effects in these patients with severe dystonia and low motor abilities.[21] As parents and children often aim for improvements in gross motor functions when considering DBS, the GMFM-66 may therefore still be a valid parameter, at least in patients with higher motor abilities.[19,22]

The WHO International Classification of Functioning, Disability, and Health Framework supports the evaluation beyond the impairment level and aims to improve daily activity and quality of life.[23] Therefore, we chose quality of life as the primary outcome parameter.[10] Although the overall change in the CPCHILD did not reach statistical significance, there was an increase in over half of our patients. Parents reported about improvements in daily activities such as dressing, positioning, or sleep due to reduction in muscle tone and hyperkinesia. This indicates meaningful DBS effects in individual patients but also resembles heterogeneity in outcome. It is of note that the CPCHILD improvement in individual patients did not correspond to changes in their BFMDRS movement scores; therefore, perception of improved quality of life does not necessarily depend on observable changes in dystonia severity. However, assessing the quality of life in these patients is difficult. As most of our patients could not answer the quality-of-life questionnaires, we relied on caregivers' perceptions of patient quality of life, which may be influenced by personal as well as contextual factors. Furthermore, the CPCHILD addresses the situation over the previous 2 weeks, which can be challenging to summarize due to movement disorder fluctuations. Interestingly, the SF-36 (not disease specific and commonly used among adult patients) revealed significant improvements in the physical health component in patients and caregivers/parents, suggesting that GPi-DBS has positive effects on certain aspects of quality of life.

To assess the effects on individual functional needs, the goal-setting methodology of the COPM was used as another patient-centered tool. The improvement in the category performance highlights the importance of identifying individual goals that are important to the patient and family and to detect meaningful changes after intervention.[8,22,24]

Balancing the benefits against the potential risks of GPi-DBS in children with DCP is challenging, considering the difficulty in predicting treatment outcomes. The intraoperative complication rate was low in our cohort. There was a distinct rate of tissue infections along the hardware, which could be attributed to the severity of the hypertonic and hyperkinetic movement disorder in DCP, with high mechanical load. Overall, the rate of SAEs was comparable to previous reports.[25] All AEs except one resolved; therefore, the risk–benefit ratio remained unchanged. Nevertheless, potential individual harms need to be considered when counseling patients and families. There seems to be a higher risk profile among younger patients with dystonia and DBS, but dystonia management becomes more difficult with.[18,26] This needs to be considered when evaluating DBS at an early development stage, when the potential of neuronal plasticity for neuromodulation is highest.[27] Whether DBS should be applied only to severely affected patients with significant functional impairment (due to the uncertainty of outcomes, the invasive procedure, and the potential risks of infection or bleeding), or whether patients with milder symptoms should also be considered, remains unanswered by our study—our patients were all severely impaired by dystonia.[13] Larger cohorts of patients need to be studied to provide more definite answers.

The main strength of this trial is the prospective, multicenter design, with a double-blind, randomized crossover after 12 months, in an exclusively pediatric cohort. Furthermore, the focus on nonmotor outcome measures such as quality of life has not yet been prospectively assessed among children with dystonia.

Study limitations include the small study population, mainly attributable to the low prevalence of DCP and rare indication of DBS in these children.[1] Most child neurologists prefer rehabilitation approaches and provision of medical aids for many years—the basic principles of DCP medical care.[2] Despite little evidence to support the use of pharmacotherapy, many patients are still treated with multiple drugs, with little or absent improvements and unwanted side effects (like in our cohort).[28] The emotional threshold to refer for DBS is high because of the uncertain prognosis and family concerns about this invasive procedure. Therefore, recruitment was difficult and prolonged.

Furthermore, different cortical and subcortical lesion patterns may also account for heterogeneity in outcome. As the indication for DBS, so far, has been

mainly preserved for pediatric patients who are severely affected with low motor abilities, structural lesions are mostly present.

Another limitation was the short follow-up and observational period during randomization. The effects of DBS can often take months or years to evolve and can last for months after DBS withdrawal.[29,30] Therefore, the impact of DBS may not become visible when stimulation is switched OFF for only 24 hours. As some children may adapt to stimulation over time—even in the absence of an obvious effect on dystonia—leading to deterioration when DBS is suddenly switched OFF, we consciously decided to choose a short crossover due to ethical considerations in the treatment of children, to protect from distracting deterioration of movements.

In summary, despite improvements in individual patients the evidence to recommend GPi-DBS as a routine therapy to improve quality of life in pediatric DCP patients is not yet sufficient. Therefore, expectations toward a meaningful improvement must be tempered when counseling families. Our findings should be investigated further in larger cohorts of patients in multicenter settings. Multidimensional assessments across the domains of the International Classification of Functioning, Disability and Health framework are required. These should include instrumented measurements and rating scales with self-selected goals and nonmotor domains that identify the needs of these patients more reliably and better reflect small but potentially significant changes after DBS intervention.[8,19,22] Comprehensive brain imaging together with clinical neurophysiological markers should be further investigated as possible predictive markers and may also be included in the assessment of potential candidates for DBS. Solid and reliable patient stratification into high- or low-responder likelihood may be answered only in large data sets from high-quality patient registries. Such data are currently collected in the German GEPESTIM consortium and the U.S.-led international PEDiDBS registry.[31,32] These steps would provide comprehensive information on DBS effects and outcome predictability in this heterogeneous population of pediatric DCP patients, who are often severely impaired and lack alternative treatment options. Furthermore, greater understanding of the mechanisms of action within the disturbed motor circuits is mandatory to enable optimal selection of DBS targets and stimulation parameters and thus improve DBS treatment for these patients.[13]

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Data Availability Statement

Legal premises and requirements: For all proposals of data sharing or analysis outside of the study team, the strict regulations of the German and European data protection laws have to be fullfilled. We would like to indicate that data protection laws from other countries may not cover the full range of German/European regulations and may therefore not be covered by the informed consent of our patients and caregivers. In this case, a potential data transfer might violate patients´ and caregivers´ individual rights, which may bear significant legal consequences. The authors encourage the idea of data sharing and meta-analysis. Despite the above-mentioned premises and legal requirements, upon request the study protocol, statistical analysis plan, and deidentified participant data will be available (text, tables, figures, and appendices, including data dictionaries) within a period of up to 36 months after publication. Proposals should be directed to anne.koy@uk-koeln.de to gain access; data requestors will need to sign a data access form and take full responsibility by acertaining that the above mentioned legal premises will be fulfilled.

Author Contributions

Anne Koy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. 1. Research project: Conception, organization, execution: Koy, Timmermann; 2. Statistical analysis: Design, execution: Hellmich and Schiller; 3. Manuscript preparation: Writing of the first draft: Koy, Timmermann; review and critique, acquisition, interpretation of data: Kühn, Huebl, Schneider, van Riesen, Eckenweiler, Rensing-Zimmermann, Coenen, Krauss, Saryyeva, Hartmann, Haeussler, Volkmann, Matthies, Horn, Schnitzler, Vesper, Garabaghi, Weiss, Bevot, Marks, Pomykal, Monbaliu, Borck, Mueller, Prinz-Langenohl, Dembeck, Visser-Vandewalle, Wirths, and the STIM-CP investigators*. All authors read and approved the final manuscript.

References

1. Sellier E, Platt MJ, Andersen GL, Krageloh-Mann I, De La Cruz J, Cans C. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Dev Med Child Neurol 2016;58(1):85–92.
2. Monbaliu E, Himmelmann K, Lin JP, et al. Clinical presentation and management of dyskinetic cerebral palsy. Lancet Neurol 2017;16(9):741–749.
3. Koy A, Lin JP, Sanger TD, et al. Advances in management of movement disorders in children. Lancet Neurol 2016;15(7):719–735.
4. Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. Lancet Neurol 2012;11(12):1029–1038.

5. Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. Mov Disord 2013; 28(5):647–654.
6. Vidailhet M, Yelnik J, Lagrange C, et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. Lancet Neurol 2009;8(8):709–717.
7. Elia AE, Bagella CF, Ferre F, Zorzi G, Calandrella D, Romito LM. Deep brain stimulation for dystonia due to cerebral palsy: a review. Eur J Paediatr Neurol 2018;22(2):308–315.
8. Gimeno H, Tustin K, Selway R, Lin JP. Beyond the Burke-Fahn-Marsden dystonia rating scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol 2012;16(5):501–508.
9. Koy A, Kühn AA, van Riesen A, et al. Effect of deep brain stimulation of the Globus pallidus internus on quality of life in young patients with Dyskinetic cerebral palsy (STIMCP): a prospective single-arm multicenter trial with a double-blind cross-over at 12-months follow-up. J Clin Trials 2017;7(4):1–9.
10. Narayanan UG, Fehlings D, Weir S, Knights S, Kiran S, Campbell K. Initial development and validation of the caregiver priorities and child health index of life with disabilities (CPCHILD). Dev Med Child Neurol 2006;48(10):804–812.
11. Murphy AM, Milo-Manson G, Best A, Campbell KA, Fehlings D. Impact of modafinil on spasticity reduction and quality of life in children with CP. Dev Med Child Neurol 2008;50(7):510–514.
12. Hill M, Armitage P. The two-period cross-over clinical trial. Br J Clin Pharmacol 1979;8:7–20.
13. Sanger TD. Deep brain stimulation for cerebral palsy: where are we now? Dev Med Child Neurol 2020;62(1):28–33.
14. Krageloh-Mann I, Helber A, Mader I, et al. Bilateral lesions of thalamus and basal ganglia: origin and outcome. Dev Med Child Neurol 2002;44(7):477–484.
15. Quartarone A, Hallett M. Emerging concepts in the physiological basis of dystonia. Mov Disord 2013;28(7):958–967.
16. McClelland VM, Fiahlo D, Flexney-Briscoe D, et al. Somatosensory evoked potentials and central motor conduction times in children with dystonia and their correlation with outcomes from deep brain stimulation of the Globus pallidus internus. Clin Neurophysiol 2018 Feb;129(2):473–486.
17. Lin JP, Lumsden DE, Gimeno H, Kaminska M. The impact and prognosis for dystonia in childhood including dystonic cerebral palsy: a clinical and demographic tertiary cohort study. J Neurol Neurosurg Psychiatr 2014;85(11):1239–1244.
18. Lumsden DE, Kaminska M, Gimeno H, et al. Proportion of life lived with dystonia inversely correlates with response to pallidal deep brain stimulation in both primary and secondary childhood dystonia. Dev Med Child Neurol 2013;55(6):567–574.
19. Haberfehlner H, Goudriaan M, Bonouvrié LA, et al. Instrumented assessment of motor function in dyskinetic cerebral palsy: a systematic review. J Neuroeng Rehabil 2020;17(1):39
20. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 1985;35(1):73–77.
21. Tustin K, Elze MC, Lumsden DE, Gimeno H, Kaminska M, Lin JP. Gross motor function outcomes following deep brain stimulation for childhood-onset dystonia: a descriptive report. Eur J Paediatr Neurol 2019;23(3):473–83.21.
22. Lumsden DE, Gimeno H, Tustin K, Kaminska K, Lin JP. Interventional studies in childhood dystonia do not address the concerns of children and their carers. Eur J Pediatr Neurol 2017;21(1): 147–167.
23. Gimeno H, Lin JP. The international classification of functioning (ICF) to evaluate deep brain stimulation neuromodulation in childhood dystonia-hyperkinesia informs future clinical & research priorities in a multidisciplinary model of care. Eur J Paediatr Neurol 2017;21(1):147–167.
24. Gimeno H, Tustin K, Lumsden D, Ashkan K, Selway R, Lin JP. Evaluation of functional goal outcomes using the Canadian occupational performance measure (COPM) following deep brain stimulation (DBS) in childhood dystonia. Eur J Paediatr Neurol 2014;18(3): 308–316.
25. Kaminska M, Perides S, Lumsden DE, et al. Complications of deep brain stimulation (DBS) for dystonia in children - the challenges and 10 year experience in a large paediatric cohort. Eur J Paediatr Neurol 2017;21(1):168–175.
26. Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: experience and technical pearls. J Neurosurg Pediatr 2011; 8(6):566–574.
27. Ismail FY, Fatemi A, Johnston MV. Cerebral plasticity: windows of opportunity in the developing brain. Eur J Paediatr Neurol 2017; 21(1):23–48.
28. Lumsden DE, Kaminska M, Tomlin S, Lin JP. Medication use in childhood dystonia. Eur J Paediatr Neurol 2016;20(4):625–629.
29. Ruge D, Cif L, Limousin P, et al. Longterm deep brain stimulation withdrawal: clinical stability despite electrophysiological instability. J Neurol Sci 2014;342(1–2):197–199.
30. Romito LM, Zorzi G, Marras CE, Franzini A, Nardocci N, Albanese A. Pallidal stimulation for acquired dystonia due to cerebral palsy: beyond 5 years. Eur J Neurol 2015;22(3): 426–e32.
31. Koy A, Weinsheimer M, Pauls KA, et al. German registry of paediatric deep brain stimulation in patients with childhood-onset dystonia (GEPESTIM). Eur J Paediatr Neurol 2017;21(1):136–146.
32. Marks W, Bailey L, Sanger TD. PEDiDBS: the pediatric international deep brain stimulation registry project. Eur J Paediatr Neurol 2017;21(1):218–222.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.