BRIEF REPORT

# Long-Term Follow-Up of Pediatric Patients with Dyskinetic Cerebral Palsy and Deep Brain Stimulation

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**ABSTRACT: Background:** Deep brain stimulation (DBS) has been increasingly used in the management of dyskinetic cerebral palsy (DCP). Data on long-term effects and the safety profile are rare.
**Objectives:** We assessed the efficacy and safety of pallidal DBS in pediatric patients with DCP.
**Methods:** The STIM-CP trial was a prospective, single-arm, multicenter study in which patients from the parental trial agreed to be followed-up for up to 36 months. Assessments included motor and non-motor domains.
**Results:** Of the 16 patients included initially, 14 (mean inclusion age 14 years) were assessed. There was a significant change in the (blinded) ratings of the total Dyskinesia Impairment Scale at 36 months. Twelve serious adverse events (possibly) related to treatment were documented.
**Conclusion:** DBS significantly improved dyskinesia, but other outcome parameters did not change significantly. Investigations of larger homogeneous cohorts are needed to further ascertain the impact of DBS and guide treatment decisions in DCP. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

**Key Words:** children; deep brain stimulation; dyskinetic cerebral palsy; prospective; trial; long-term effects

## Introduction

Dyskinetic cerebral palsy (DCP) is the most common cause of acquired dystonia in childhood.[1]

Management of DCP is challenging because pharmacological treatment is often ineffective or limited by medication-related side effects.[2] Deep brain stimulation of the globus pallidus internus (GPi-DBS) has been increasingly applied in patients with DCP over the last two decades, with heterogeneous outcomes.[3,4] However, data on pediatric patients is still limited, especially for long-term outcomes.

We recently conducted the first prospective, multicenter trial on exclusively pediatric patients with DCP and GPi-DBS (STIM-CP).[5] Improvement in quality of life after 12 months of treatment (assessed by the Caregiver Priorities & Child Health Index of Life with Disabilities (CPCHILD) questionnaire) was chosen as the primary outcome parameter. Despite improvements in some patients, significant changes in CPCHILD and dystonia/chorea severity were not achieved. As the effects of DBS in patients with acquired dystonia can be prolonged, with reports of further improvement beyond 1 year of treatment,[4] we conducted an open-label extension of the STIM-CP trial.

## Methods

### Study Design

STIM-CP was a multicenter, single-arm, pre-post trial using a within-patient control to document outcomes for bilateral GPi-DBS in the treatment of DCP for up to 36 months (NCT02097693) (Table S1).[6]

The extension of the original study protocol conformed with the Helsinki Declaration and Good Clinical Practice Guidelines and was approved by the ethics committees of Cologne (13–359; trial protocol code Uni-Koeln 1603) and by each of the participating centers. Seven clinical sites were involved in Germany. Source data verification, data management, serious adverse events (SAE) and project management were done by the Clinical Trials Centre Cologne, Germany.

### Participants

Pediatric patients diagnosed with DCP due to perinatal asphyxia who were undergoing GPi-DBS were recruited between February 28, 2014, and April 4, 2019. Patients were eligible when they met the following main inclusion criteria: age 7–18 years, acquired dystonia with a history of perinatal hypoxic brain injury, bilateral GPi-DBS chosen for treatment, posteroventral lateral GPi and motor thalamus mostly intact on latest MRI. Main exclusion criteria were inherited or idiopathic dystonia, severe axial hypotonia with loss of head control, fixed hemi-dystonia, severe spasticity, fixed skeletal deformations with loss of function, and other severe concurrent neurological disease.

### Outcomes

During the parental trial, patients were assessed at baseline, 6- and 12-months follow-up for ratings of quality of life (CPCHILD), severity of dystonia (BFMDRS movement [−M] and disability [-D] scores), severity of dyskinesia (dyskinesia impairment scale [DIS]), quality of life (short form [SF]-36), mood (Strength and Difficulties Questionnaire [SDQ]), speech (Frenchay Dysarthria Assessment [FDA]), and pain (Wong Baker Faces). Caregivers were also assessed for quality of life (SF-36) and their burden of care (Family Burden [FaBel]). For the extension trial patients and caregivers were re-assessed using the same tests at 24 and 36 months. All assessments were done under continuous neurostimulation.

All BFMDRS-M and DIS ratings were performed by three blinded external movement disorders experts (EM, AH, WM), based on videos and according to standardized protocols.

### Safety

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

assessment. SAEs were defined as any events that led to death, disability, hospital admission, or lengthened a hospital stay.

### Data Sharing

Upon reasonable request, the study protocol, statistical analysis plan, and deidentified participant data will be available for 36 months after publication.

## Results

Fourteen of the initial 16 patients who agreed to the study extension attended the 36 months follow-up (Tables S2–S4). Two patients dropped out; the hardware system was removed in one patient because of ongoing infection, while the other patient declined study continuation.

### Outcome Parameters

The effects of long-term GPi-DBS on quality of life, severity of dystonia, and chorea are illustrated in Fig. 1.

There were significant changes in the (blinded) ratings of the DIS. At 24 and 36 months, respectively, the DIS total score improved from baseline by 34.9 (95% CI −0.2 to 69.9) points ($P = 0.051$) and 32.0 (95% CI 2.0 to 62.0) points ($P = 0.038$). At 36 months, the sub-score "chorea at rest" (DIS-C) improved by 8.2 (95% CI 1.2 to 15.3) points ($P = 0.026$). There were no significant changes in the BFMDRS motor or disability scores, CPCHILD, or in any other parameters (Table S5).

Differentiating between younger (≤12 years, n = 6) and older (>12 years, n = 8) patients, differences in the DIS and BFMDRS-M scores were obtained in the mixed model analysis (Fig. S1). In patients up to 12 years of age the improvement in the BFMDRS-M at 24- and 36-months was significantly greater compared to older patients ($P = 0.035$ and $P = 0.039$, respectively). The younger patients also showed more improvement in the DIS total score after 24 months ($P = 0.08$), whereas both age groups were similar after 36 months.

### Adverse Events

From implantation to 36 months, 12 SAEs (in nine patients) and 19 AEs related or possibly related to surgery, device and/or stimulation were documented (Table 1). There were fewer (possibly) treatment-related (severe) AEs in younger (age at surgery ≤12 years) than in older (>12 years) patients (SAEs 2 vs. 10, AEs 5 vs. 14, respectively).

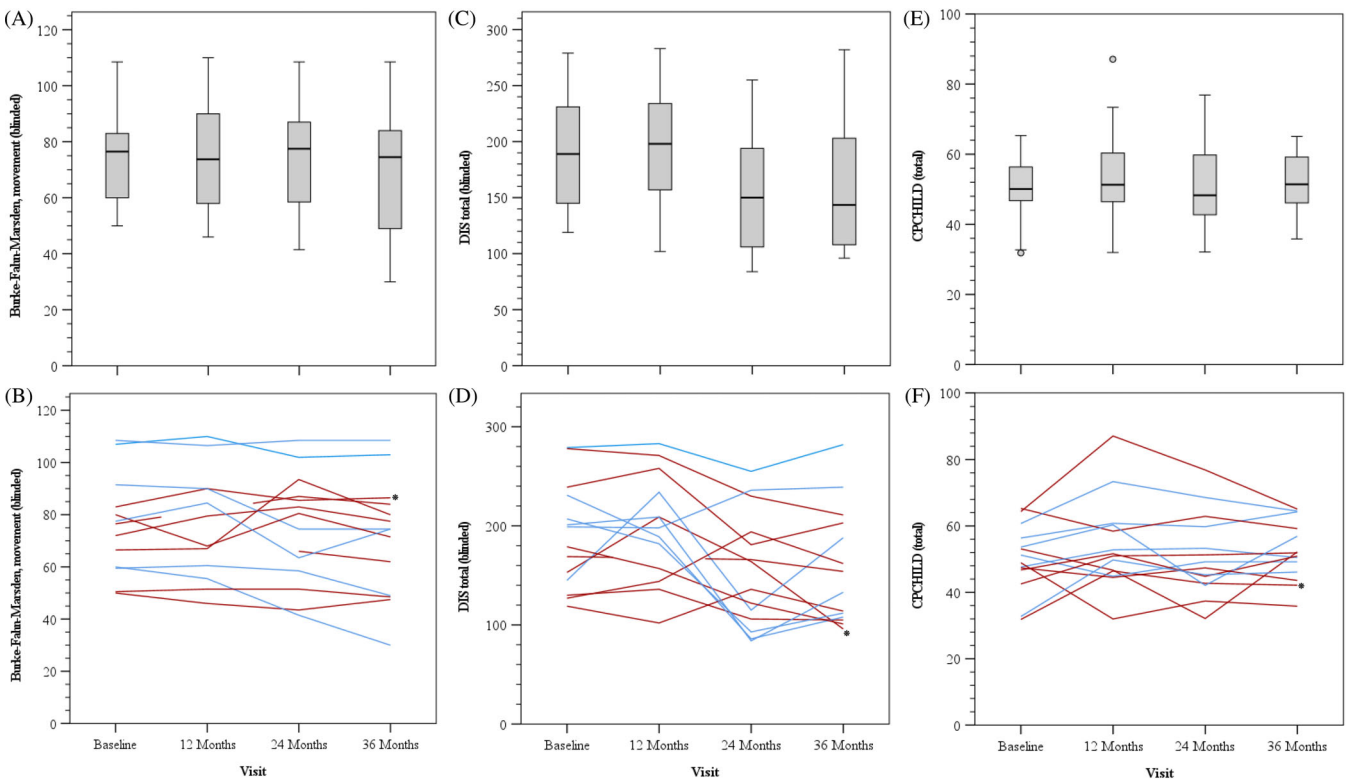


**FIG. 1.** Burke-Fahn-Marsden Dystonia Rating Scale movement score (A, B), Dyskinesia Impairment Scale (DIS) total score (C, D), and Caregiver Priorities & Child Health Index of Life with Disabilities (CPCHILD) (E, F) before surgery (baseline), 12, 24, and 36 months after surgery (blue lines: patients ≤12 years; red lines: patients >12 years; the patient marked by * was treated with clonidine at 36 months). [Color figure can be viewed at wileyonlinelibrary.com]

**TABLE 1** *Adverse events (AEs) and serious adverse events (SAEs) by relatedness; occurrence from implantation to 36 months follow-up. All SAEs required hospital admissions. Terms were adapted from the medical dictionary for regulatory activities (MedDRA) coding system*

| (Severe) adverse events | Recovered without sequelae | Not yet recovered/ unknown |
|---|---|---|
| SAEs (possibly) related to surgery, device and/or stimulation | 12 | 0 |
| Febrile seizure[a] | 1 | 0 |
| Device use error[b] | 1 | 0 |
| Dyskinesia aggravated[c] | 3 | 0 |
| Intracerebral hemorrhage | 1 | 0 |
| Fever | 1 | 0 |
| Medical device replacement[d] | 5 | 0 |
| AEs (possibly) related to surgery, device and/or stimulation | 19 | 2 |
| Device use error | 5 | 1 |
| Dyskinesia aggravated | 5 | 1 |
| Fatigue | 1 | 0 |
| Headache | 5 | 0 |
| Hypersalivation | 1 | 0 |
| Scar pain | 1 | 0 |
| Seroma | 1 | 0 |
| SAEs not related to device and/or stimulation | 6 | 0 |
| Broken wrist | 1 | 0 |
| Cheek swelling | 1 | 0 |
| Headache | 1 | 0 |
| Fever | 1 | 0 |
| Drug intoxication (benzodiazepine) | 1 | 0 |
| Rhonchopathy | 1 | 0 |
| AEs not related to device and/or stimulation | 24 | 2 |
| Blistering | 1 | 0 |
| Dislocation of joint | 1 | 1 |
| Dyskinesia aggravated | 1 | 0 |
| Fall | 1 | 0 |
| Infection respiratory | 11 | 0 |
| Fungal infection | 1 | 0 |
| Headache | 2 | 0 |
| Muscle disorder | 1 | 0 |
| Nose injury | 1 | 0 |
| Product size issue (seat shell defect) | 0 | 1 |
| Reduced general condition | 1 | 0 |
| Fever | 1 | 0 |
| Diarrhoea | 1 | 0 |
| Pain | 1 | 0 |
| All SAEs and AEs | 61 | 4 |
| Related to surgery, device and/or stimulation | 31 | 2 |
| Not related | 30 | 2 |

*Note*: Data shown are frequencies of adverse events which occurred in all 16 patients initially implanted in the STIM-CP trial.
[a]Documented as "possibly related to stimulation".
[b]Due to accidental switching off the device.
[c]Occurred all in one patient due to adjustments of stimulation settings by the caregivers, and due to an accidental switching off the device.
[d]Due to tissue infection along the extension lead (n = 1), disconnection of the extension lead (n = 1), and technical defects of the implantable pulse generator (n = 2), implant site infection (n = 1; drop out after 12 months follow-up).

## Discussion

To our knowledge, this is the first prospective trial in a multicenter setting to investigate the long-term effects of GPi-DBS on motor and non-motor outcomes in pediatric DCP patients. The STIM-CP cohort confirmed that the mean treatment response in patients with acquired dystonia is less and more heterogeneous compared to patients with certain forms of inherited dystonia.[7-9] However, there were significant improvements in the DIS scores over 36 months, which were not evident after the first postoperative year, indicating a potential but delayed DBS effect on the hyperkinetic movements. This is in line with previous observations suggesting that the mobile elements are more responsive to DBS than the tonic parts in patients with dystonia, and that the maximum therapy effects may not be visible until the second year of treatment, which may be attributed to long-term changes in plasticity in these young patients.[4,10-12]

Interestingly, younger patients (≤12 years) seemed to benefit more than older patients with respect to DIS at 24 months and BFMDRS-M at 24 and 36 months. Although DCP is regarded as a static neurological disorder, symptoms progress in most of the patients due to prevailing increased muscle tone and dystonia management becomes more difficult with increasing age.[13,14] Therefore, DBS could be considered at an early stage of

development, when plasticity is greatest,[15] to restrict aggravation of musculoskeletal complications over the long-term.

The reasons for discrepancies in treatment outcomes in DCP patients seem to be multifactorial and have been discussed before.[5] Patients with DCP are often heterogeneous in terms of clinical presentation, etiology, and structural brain abnormalities.[16,17] Although, we aimed for a highly-selective cohort, the clinical phenotype was still broad, comprising hyper- and hypokinetic movement disorder components with a varying degree of spasticity, and various structural brain lesions. There was no clear correlation between the extent of the lesions and outcome scores, however, the pattern of structural lesions together with review of the electrode positions may be a potential outcome predictor and needs to be further explored in larger cohorts.

The high level of impairment may also have limited the outcomes. Most patients were classified as GMFCS level IV or V before implantation. According to previous data, the severity of dystonia negatively correlates with outcomes.[18] Whether DBS should therefore be offered to patients with milder symptoms and higher motor abilities could be considered, but remains unanswered by our study.

Etiology can also affect treatment response. As most CP patients are diagnosed by clinical characteristics and perinatal or infantile medical history, some patients may have other underlying genetic or metabolic disorders mimicking a CP phenotype.[19,20] Some of these disorders require specific treatments, and do not benefit from DBS.

Heterogeneity in outcomes may also be attributed to differences in assessment approaches. Most trials investigating DBS in patients with dystonia focus on clinical ratings scales such as the BFMDRS.[10] However, DCP patients are often severely impaired by distracting hyperkinetic movements, so the DIS was also introduced. Its improvement while the BFMDRS remained unchanged at 36 months, indicates that the BFMDRS may not be sensitive enough to capture motor changes relevant to these patients.

We also included parameters for quality of life, pain, and burden of caregivers, as these are often the main issues addressed by parents and patients when considering treatment interventions such as DBS.[21,22] As quality of life improved in some patients and caregivers but failed to reach statistical significance in the long-term, this trend needs to be investigated further in larger cohorts.

The overall risk profile was moderate and comparable to previously-reported case series.[23,24] Unlike the very low intraoperative risk profile,[5] there was a considerable number of complications such as hardware replacements during long-term follow-up, which mean significant individual harm to the children. This needs to be considered when counseling patients and families.

The main strength of our study is the prospective, multicenter design, with a long-term follow-up of motor and non-motor outcomes after DBS, including DIS, in an exclusively pediatric cohort.

Study limitations include the small study population, mainly attributable to the low prevalence of DCP and the even rarer indication for DBS, the broad range of ages (8–18 years), as well as the heterogeneity in clinical phenotype.

In summary, there is a significant improvement in dyskinesia in this cohort of young patients with DCP under chronic neurostimulation over the long–term. Although the reduction in dyskinesia can have a relevant impact on daily activities for individual patients, this improvement was not reflected in quality of life and carer burden assessments. Therefore, the evidence to recommend GPi-DBS as a routine therapy in pediatric DCP patients is not yet sufficient, and the indication for DBS still needs individual evaluation. Nevertheless, in view of the limitation of alternative pharmacological treatment approaches in DCP, neuromodulation may be the only potentially effective treatment option in the future for these often severely disabled patients. Therefore, the effects of DBS need to be further investigated in larger, clinically-homogeneous cohorts of patients in multicenter settings. Instead of standardized clinical impairment scales, individualized treatment goals should be defined and implemented to assess relevant DBS effects in these patients.

Furthermore, a better understanding of the mechanisms of action within the disturbed motor networks using advanced imaging techniques is mandatory, to enable optimal selection of DBS targets and individual stimulation parameters.

## Author Contributions

Anne Koy and Lars Timmermann developed the study design, wrote the first draft of the manuscript and verified the underlying data. Petra Schiller wrote the statistical analysis plan, performed the statistical analysis and has been involved in drafting the manuscript. Andrea A. Kühn, Julius Huebl, Gerd-Helge Schneider, Matthias Eckenweiler, Cornelia Rensing-Zimmermann, Volker Arnd Coenen, Joachim K. Krauss, Assel Saryyeva, Hans Hartmann, Delia Lorenz, Jens Volkmann, Cordula Matthies, Alfons Schnitzler, Jan Vesper, Alireza Gharabaghi, Daniel Weiss, Andrea Bevot, Warren Marks, Angela Howser, Elegast Monbaliu, Joerg Mueller, Reinhild Prinz-Langenohl, Veerle Visser-Vandewalle, and the STIM-CP investigators made substantial contributions to the conception, design, and conduction of the trial, and have been involved in

drafting the manuscript or revising it critically for important intellectual content. All authors read and approved the final manuscript.

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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.

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# Supporting Data

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