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Effect of Deep Brain Stimulation of the Globus Pallidus Internus on Quality of Life in Young Patients with Dyskinetic Cerebral Palsy (STIM-CP): a Prospective Single-Arm Multicenter Trial with a Double-Blind Cross-Over at 12-Months Follow-up

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Abstract

Introduction: Deep brain stimulation of the globus pallidus internus (GPi-DBS) can be effective in patients with dyskinetic cerebral palsy (CP), but outcome in terms of dystonia severity is often less pronounced and more variable compared to patients with inherited monogenic dystonia. A few published case series encompassing retrospective data have shown that GPi-DBS is associated with favorable quality of life outcomes, even in patients without changes in the BFMDRS, suggesting that the sole use of clinical rating scales may not reflect the full effects of DBS, especially not in patients with acquired forms of dystonia such as dyskinetic CP. However, there is no prospective data on DBS effects in children.

Methods: This is a prospective single-arm study to investigate the effects of GPi-DBS in young patients with dyskinetic CP. 20 patients aged 7-18 years will be recruited in a multicenter setting. 12 months after lead implantation patients are randomized by a double-blind cross-over into two groups: One group starts with ongoing stimulation, in the other group stimulation is turned off. After 24 h they switch stimulation settings. Dystonia severity will be assessed at the end of each phase.

We hypothesize an improvement in quality of life by GPi-DBS. Therefore, the mean change in the CPCHILD questionnaire from baseline to 12 months is chosen as the primary outcome parameter. Secondary outcome parameters encompass dystonia severity, motor function, speech, mood, cognition, pain, and quality of life of the carers before and up to 36 months after implantation.

Discussion: This is the first prospective trial investigating the effects of GPi-DBS on motor and non-motor outcome in a cohort of exclusively pediatric patients in a multicenter setting. Furthermore, long-term data on effects and side effects of GPi-DBS in young patients with dyskinetic cerebral palsy will be generated.

Keywords: Deep brain stimulation; Dyskinetic cerebral palsy; Children, Quality of life; Prospective trial

Introduction

Several case reports and case series provide evidence in support of the effectiveness of deep brain stimulation of the globus pallidus internus (GPi-DBS) in a large proportion of patients with dyskinetic cerebral palsy (CP) [1-6]. However, outcome in terms of dystonia severity is often less pronounced and more variable compared to DBS in patients with isolated inherited dystonia [3,7]. A few published outcome studies have also shown that GPi-DBS is associated with favorable quality of life outcomes, even in patients without changes in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). Therefore, the sole use of clinical rating scales does not reflect the full effect of DBS, especially not in patients with acquired forms of dystonia such as dyskinetic CP [8-10].

Long-term outcome reports are mostly limited to cohorts of adult patients [6,7,11]. Most reports encompass retrospective data generated by single center settings, except only one trial investigating the effects of GPi-DBS in a cohort of adult patients in a prospective follow-up design over 12 months [2]. There is no prospective data on DBS exclusively in children. Therefore, in order to further contribute to the body of evidence on DBS in young patients with acquired dystonia, we are conducting this prospective study to investigate the effects of GPi-DBS specifically on quality of life in a larger cohort of pediatric patients with dyskinetic CP. Data of this study will provide detailed information about effects on different outcome parameters and effect sizes and provides the first prospective data set on DBS in children generated by a multicenter setting. This will render fundamental knowledge for larger randomized trials on pediatric DBS for dyskinetic CP in the future.

Primary and Secondary Study Questions

Primary study question

There can be a large discrepancy between effects subjectively perceived by patients or care givers and changes assessed by dystonia scales. Therefore this study is highly focusing on patient-related outcome measures implementing the Caregiver Priorities and Child Health Index of Life with disabilities (CPCHILD) questionnaire as an age-related validated questionnaire on quality of life of patients with cerebral palsy [12,13]. The CPCHILD measures caregivers´ perspectives on the health status, comfort, wellbeing, functional abilities, and ease of caregiving to children with severe disabilities. It was developed to measure the effectiveness of interventions intended to improve or preserve the outcomes for children with severe disabilities, including non-ambulant children with severe cerebral palsy. The CPCHILD covers many areas of daily activities, which are essential for patients with CP. Therefore we chose the mean change in the CPCHILD from baseline (V0) to 12 months (V5) after the first lead implantation as the primary outcome parameter. Our hypothesis is an improvement of quality of life of at least 10% 12 months after implantation [14].

Secondary study question

The secondary objectives of this study are to document patient outcomes regarding quality of life, dystonia, motor function, activities of daily living, speech, pain, cognition and affection of pediatric patients with dyskinetic CP as well as quality of life of carers up to three years after implantation. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was chosen as this is the most commonly applied clinical scale to assess dystonia in patients with cerebral palsy according to previous publications [1].

Study design

The study has a multicenter, single-arm, pre-post design using a within-patient control (each patient serves as his/her own control) to document patient outcomes for the implantable VerciseTM-DBS system by Boston Scientific for bilateral GPi-DBS in the treatment of dyskinetic CP up to three years after implantation. After the 12 months follow-up visit (12-MFU, V5) a randomized double-blind cross-over is implemented for two days to investigate, whether dystonia and dyskinesia change after the stimulation is switched off for 24 h (Figures 1 and 2).

A maximum of 20 patients will be recruited. Enrolment is across 12 study sites with an initial maximum of 4 patients enrolled at any one site.

Methods

Study procedure

If the medical indication for bilateral GPi-DBS for the treatment of dyskinetic CP has been provided, patients are screened for study participation. Only patients who will be implanted by the VerciseTM-DBS-System can be recruited for the trial as this was the only DBS-system which was approved for the treatment of acquired dystonia from the age of 7 years at the time the trial has started in 2014. The screening visit must be completed 4-2 weeks before baseline evaluation (V0) and maximum eight weeks before implantation (for assessments see Table 1). The implantation visit (V1) should be scheduled within two weeks after first lead implantation. At 3-MFU (V2) and 9-MFU (V4) the participating study sites can decide whether these two visits can either be performed as telephone visits or outpatient appointments. For 6-MFU (V3), 24-MFU (V6) and 36-MFU (V7) patients are seen as outpatients according to the clinical routine of each center. These visits last about two to three hours. For the 12-MFU and

the succeeding randomized double-blind cross-over patients are admitted to the ward for about 4-5 days.

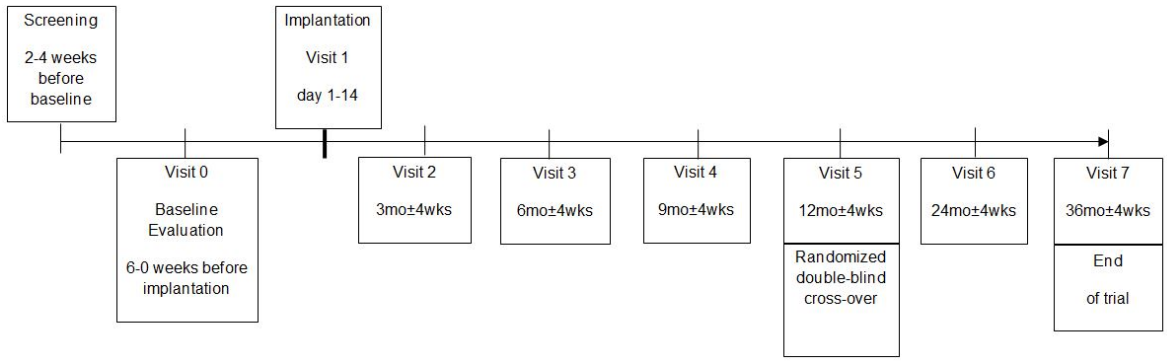

Figure 1: Study protocol: After enrolment and baseline evaluation, patients are bilaterally implanted with DBS electrodes in the GPi. There are seven postoperative follow-up visits (MFU) up to 36 months after DBS implantation. At 12-MFU (V5) patients are randomized for a double-blind cross-over for 48 h. Depending on randomization, patients receive therapeutic stimulation or not.

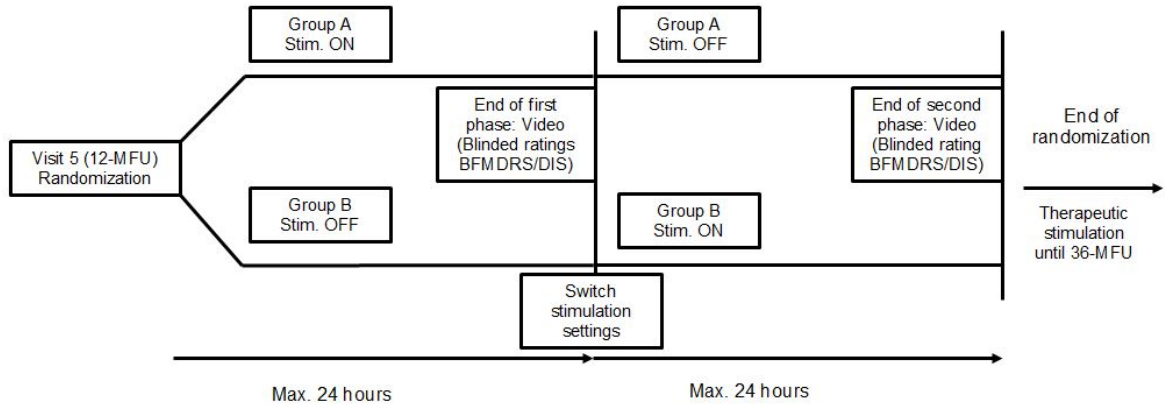

Figure 2: Double-blind cross-over: At 12-MFU (visit 5), patients will be randomized into two groups (group A: stimulation first ON, then OFF; group B: stimulation first OFF, then ON). After taking video patients switch stimulation settings after 24 h (end of first phase). Before unblinding a second video will be taken after 48 h (end of second phase).

	Study duration									
	Screening	**Base-line**	**Implantation**	**3-MFU**	**6-MFU**	**9-MFU**	**12-MFU**	**12-MFU R1+2**	**24-MFU**	**36-MFU**
Visit		0	1	2	3	4	5		6	7
CPCHILD	X	X			X		X*		X	X
BFMDRS M&D		X			X		X		X	X
Blinded Rating of BFMDRS (video)		X					X	X	X	X
GMFCS		X					X		X	X
GMFM-66		X					X			
Tardieu Scale		X					X			

Dyskinesia Impairment Scale		X					X	X	X	X
SF-36 patient		X			X		X		X	X
SF-36 carer		X			X		X		X	X
FaBel carer		X			X		X		X	X
Frenchay Dysarthria		X					X		X	X
SON-R 51/2-17yr		X					X			
ANT		X					X			
NVLT		X					X			
SDQ		X					X		X	X
COPM		X					X			
Wong Baker Faces		X			X		X		X	X
CGI		X			X		X			
Medication		X					X		X	X
Adverse Events		X	X	X	X	X	X		X	X

Table 1: Schematic overview of study procedures before implantation and at follow-up visits (MFU). The randomization phase is indicated by R1=first phase, R2=second phase. *Primary endpoint: Change in the CPCHILD score 12 months after implantation.

DBS implantation and programming

The DBS implantation itself is not part of this trial. The target of the DBS electrodes is the bilateral posteroventral lateral part of the GPi. As DBS is a well-established therapy, the treating neurosurgeons have developed their own best procedures and practices for implantation. Therefore, the surgical procedure will be performed according to the clinical standards of the participating centers.

For initial programming, the frequency should be set between at 90 and 120 Hz, and pulse width between 90 and 240 μs according to common clinical practice. The initial contacts should be the lowest two contacts (1 and 2 for left and 9 and 10 for right brain hemisphere, respectively). Only if side effects occur, more proximal contacts can be used. Continuous stimulation should be provided. The amplitude with the best effect and fewest side effects is chosen. Patients may have as many clinic visits as required for optimization of the programming, with the goal of optimizing therapy by 6-MFU. The range of stimulation parameters can be extended above or below the initial range to the full parameter ranges available on the device in order to reduce adverse effects of undesired collateral stimulation and to improve ineffective therapy. This is in the hands of the treating physician.

To achieve sufficient stimulation, the patients should be regularly tested with increasing mAmpere on all therapeutic contacts until stimulation-induced side effects occur. Only the energy level (mA) should be tested [15]. It is of note, that children sometimes report side effects at rather low voltages.

Randomization

After finishing the 12-MFU patients are randomized into two groups (group A and B) by a double-blind cross-over (neither the patient nor the treating physician know whether the patient is stimulated or not) according to numbered, sealed envelopes, which are opened sequentially for each enrolled patient by the unblinded study nurse. In group A stimulation is ongoing and then switched off, whereas in group B stimulation is switched off first and then switched on again. Randomization is block-restricted and stratified by study site. The length of each phase (day 1 and day 2) is 24 h. At the end of each phase a videography is performed according to a standardized protocol (Figure 2). Videos are rated by blinded experts on movement disorders to assess changes in severity of dystonia (BFMDRS) and dyskinesia (DIS) during the "on"- and "off"-condition.

If patients do not tolerate the stimulation settings during the cross-over, a video has to be recorded before unblinding. After taking the video the application of a short lasting benzodiazepine could be tried to release dystonia and to motivate patients to continue. If patients still refuse to carry on, unblinding is permitted, which does not imply exclusion from the study. After the cross-over, the contacts with the best effects and fewest side effects can be freely chosen for further treatment.

Population, screening and recruitment

Up to 20 patients diagnosed by dyskinetic CP due to perinatal asphyxia undergoing GPi-DBS will qualify for the evaluable population. The diagnosis of perinatal asphyxia is based on the neonatal history, including objective parameters such as core blood gases, base deficiency and 5´-APGAR score, and on the clinical details about the disease course. If there are any uncertainties about the

etiology of dystonia because medical history is incomplete or symptoms seem to be progressive, diagnostic investigations will be completed to safely exclude other causes before inclusion in the trial.

12 university clinics (study sites) will be involved. Within a clinic the Departments of Pediatric Neurology, of Neurosurgery/Functional and Stereotactic Neurosurgery and of Neurology will be involved in the interdisciplinary treatment of patients. Patients will be generally recruited by social pediatric centers, or departments of neurology, child neurology and neurosurgery over a period of 3.5 years.

Inclusion and exclusion criteria

Subjects who meet all of the following criteria may be given consideration for inclusion in this clinical trial, provided no exclusion criteria are met.

Inclusion criteria are-

i) GPi-DBS has been chosen for the treatment of dystonia.

ii) Aetiology of dystonia is dyskinetic cerebral palsy due to perinatal hypoxic brain injury.

iii) Age at enrolment 7-18 years.

iv) Globus pallidus internus (pars posterior) and thalamus (motor part) intact on MRI.

Exclusion criteria are-

i) Patients with the typical DYT1-causing TOR1A mutation (c. 907_909delGAG) [16] or other forms of inherited or idiopathic dystonia.

ii) Severe axial hypotonia with total loss of head control (e.g. absence of control at "upper thoracic level" in the SATCo score) (medication effect excluded).

iii) Fixed hemi-dystonia.

iv) Fixed severe skeletal deformations with loss of function requiring immediate intervention by orthopedic surgery.

v) Severe spasticity in knee- and elbow-flexors and -extensors (Modified Ashworth Scale >3).

vi) Conditions likely to require use of MRI in the future.

vii) Any history of frequent grand-mal seizures without response to anticonvulsive treatment.

viii) Participation in another interventional trial.

Outcome measures

The primary endpoint of this study is improvement in quality of life, assessed by the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD) 12 months after implantation [12-14]. The questionnaire can also be answered by the patient himself. The CPCHILD consists of 36 items over 6 domains (activities of daily living/personal care (8 items), positioning, transfer and mobility (8 items), comfort and emotions (9 items), communication and social interaction (7 items), health (3 items) and overall quality of life (1 item).

Secondary endpoints comprise severity of dystonia (BFMDRS), motor function and degree of disability (Gross Motor Function Classification Measure/GMFCS, Gross Motor Function Measure/GMFM-66), severity of spasticity (Tardieu), severity of dyskinesia (Dyskinesia Impairment Scale/DIS), speech and language (Frenchay Dysathria), quality of life of patients and carers (SF-36), cognitive function (Snijders-Oomen-Non-Verbal Intelligence Test/SON-R 51/2-17), attention (Attention Network Test/ANT), memory (Non-verbal learning test/NVLT), mood (Strength and Difficulties Questionnaire/SDQ), priority tasks of daily living (Canadian Occupational Performance Measure/COPM), pain perception (Wong Baker Faces), and Clinical Global Impression/CGI [17-29].

Patients are encouraged not to undergo surgical interventions such as the implantation of an intrathecal baclofen pump or to start injections of botulinum toxin for the first time during the first 12 months of the trial to avoid other factors with potential influence on the primary outcome parameter.

Changes in medication (class of substance and total dosage/day) will be documented at each visit.

Withdrawal from the study

While study withdrawal is discouraged, patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. The reasons for withdrawal must be documented in the clinical side file. Withdrawn patients will not undergo any additional investigational follow-up and will be treated according to clinical routine. Only the patients who withdraw prior to implantation will be replaced. The withdrawn subject will undergo a final examination (final visit) which must be documented. Patients will be discontinued for the following reasons: Withdrawal of consent, study non-compliance, occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Sample size and power calculation

Quality of life is obtained as a continuous response variable from study subjects. Prior data on changes in quality of life assessed by the CPCHILD in a cohort of pediatric patients with CP before and after intervention by pharmacotherapy indicate that the difference (pre to 12 months post) is normally distributed with standard deviation of 12.6 [12]. If the true difference in the mean response of the CPCHILD is at least 10 (reliable change is based on Narayanan et al.), we will need to study 16 subjects to be able to reject the null hypothesis that the mean difference is zero with probability (power) of 0.85 (paired t-test) [14]. The type I error probability associated with this test of this null hypothesis is 0.05 (two-sided). To account for up to 20% attrition, 20 patients will be included.

Statistical analysis

Statistical methods to be used include contingency table analysis, descriptive methods (e.g. mean, standard deviation; graphs), linear mixed models and time-to-event methods (Kaplan-Meier estimation). Data from all included patients will be subjected to statistical analysis. The primary analysis comprises the patients treated and observed per protocol, i.e. patients will be excluded when protocol required visits/assessments are out of window, and the visit is missed at 12 months.

An analysis of all included patients will be considered secondary (intention-to-treat approach).

Continuous variables will be summarized by valid n, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum, categorical variables by counts and percentages. Confidence intervals (95% level) will be calculated wherever they might support interpretation. The cross-over data will be analyzed by the Hills-Armitage approach [30]. Statistical analyses will be done using SPSS Statistics software (IBM Corp., Armonk, New York, USA).

The change in the primary variable CPCHILD from-6-0 weeks (preoperative) to 12 months will be analyzed by a paired t-test at two-sided level of 5% (H0: expected change=0 *vs.* HA: expected change ≠ 0). For secondary analysis, mixed models for repeated measures (MMRM) are used to estimate contrasts over time (per protocol, intention-to-treat) taking incomplete observations into account. A responder analysis (response=improvement of ≥ 10%) and time-to-event approaches (Kaplan-Meier curves) will be added (e.g. time to and duration of response). The secondary variables will be analyzed along the same lines as the primary variable.

Association of response to DBS (continuous/dichotomized) with age, age at disease onset, disease duration (i.e. interval from onset of dystonic symptoms to DBS implantation), structural brain lesion, severity of dystonia (BFMDRS), distribution and type of movement disorders will be explored by multiple regression models (linear, logistic, Cox) as far as limited by the sample size.

Technical data about the device such as electrode localization and parameter settings, age at surgery (younger patients aged ≤ 12years versus older patients), gender and severity of dystonia and dyskinesia will be used for exploratory analysis.

Quality assurance/monitoring

Monitoring is performed by Clinical Trials Center Cologne (CTC-Cologne). Monitors inspect the participating study centers regularly to ensure implementation of the study protocol and high quality of documentation. An initiation visit, 2 regular visits and a close-out visit are performed. Original source documents are reviewed for verification of data in the case report form. For each patient the presence of written consent is checked and the inclusion and exclusion criteria are controlled.

Data management

IT infrastructure and data management are provided by the CTC Cologne. The data management system is based on commercial trial software and includes a database. The trial database was developed and validated before data entry based on standard operating procedures at the CTC Cologne. Each center enters the data into a validated trial database, and the data entered is compared and reconciled afterwards by the CTC monitoring. Plausibility checks are also conducted in the database. Discrepancies and implausible values are clarified in writing between the data manager and the trial site. The trial site has to answer these queries without unreasonable delay. Further details will be specified in the data management manual. After completion and cleaning of data, the database is locked and the data exported for statistical analysis. ECRFs, consent forms and other information relevant to the trial will be archived for 10 years in accordance with 13 Section 10 of the GCP Regulations.

Safety

The Vercise™-DBS-System is CE-marked for acquired dystonia in patients 7 years or older. As CP is the most common cause for acquired dystonia, the medical device will only strictly be used within the medical indication.

The monitoring of adverse events (AEs/SAEs) will start with the day of implantation of the medical device and will end latest 4 weeks after the final assessment (visit 7). AEs/SAEs are documented at the scheduled and unscheduled clinical visits. All incidents are reported to the regulatory authority. All safety-relevant events are promptly reported to the ethics committee and the safety monitoring committee, that is independent from the sponsor and competing interests (Prof. W. Lehmacher, former director of the Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne; Prof. J. Mueller, Head of Department of Neurology, Vivantes Klinikum Spandau; Prof. F. Alesch, Department of Neurosurgery, University of Vienna). Important protocol modifications will be communicated to all relevant parties (investigators, ethics committee, trial participants, safety monitoring committee).

Ethics and Consent

The trial (protocol version 01-18 date: December 7, 2013, Amendment 1: January 6, 2016) has been approved by the ethics committee of Cologne (trial protocol code Uni-Koeln-1603) and by the local ethics committees of the participating centers. All patients give their written consent to participate in the trial.

Different consent forms according to age (7-11 years, 12-17-years, adult patients) have been developed. All patients give written informed consent if they are capable of understanding the content of the trial. Care givers also give their written informed consent before study participation, if their children are underage or not capable to understand the study content. There are separate consent forms for genetic testing of the typical DYT1-causing *TOR1A* mutation (c. 907_909delGAG) to exclude the most common inherited form of dystonia, and for the assessment of quality of life of the carers [16].

Study Registration

The clinical trial is registered at ClinicalTrials.gov(NCT02097693, registration date March 24, 2014). Recruitment has started at February 28, 2014 and is expected to end at October 31, 2017.

Discussion

This multi-center open-label study is the first prospective trial investigating the outcome of GPi-DBS in exclusively pediatric patients with dyskinetic CP in several domains. The prospective study design eliminates the bias associated with case selection in a retrospective review and ensures that identical procedures are followed for data capture and review. To perform a randomized controlled trial a high number of patients would be required (n>50), which is almost impossible due to the rare indication for DBS in children with acquired dystonia, and due to financial obligations. Therefore, we chose a single-arm pre-post study design which uses a within-patient control (each patient serves as his own control). To assess changes in dystonia severity objectively all videos are rated by blinded experts on movement disorders. The randomized double-blind cross-over design at 12 months after electrode implantation further contributes to the objective assessment of effects.

We have chosen a follow-up interval of 12 months to measure our primary efficacy endpoint because this period for follow-up has been commonly cited in case series and larger case series so far [2,31,32]. This time point represents a balance between allowing the patient to reach optimal therapy through changes in programming and the time a delayed surgical effect can be expected. However, it has been reported that DBS effects on dystonia in CP patients can occur with time delay. According to a recent case series of 15 adult patients with dyskinetic CP and DBS the maximum effect was not reached until a mean postoperative follow up of 1.7 years after implantation. Some patients of this cohort were assessed up to 6 years postoperatively and showed sustained effects [6]. There is hardly any data on long term outcome of children undergoing DBS. Therefore, in this pediatric cohort secondary outcome parameters will be assessed up to 36 months after implantation.

The main strengths of this study are certainly the prospective, multicenter design in an exclusive pediatric cohort, and the focus on non-motor outcome measures, which have not yet been assessed in a prospective fashion among children. Furthermore, previous studies on patients with dyskinetic CP undergoing DBS usually include the BFMDRS to assess dystonia severity. In fact, CP-patients often suffer of a complex hyperkinetic movement disorder. Therefore, STIM-CP is the first prospective trial also including the blinded rating of choreoathetosis as a symptom by using the DIS.

Potential limitations of the study are the relatively small sample size and the age range including children and adolescents, which is mainly attributed to the low prevalence of dyskinetic CP and the rare indication for DBS in these children [33]. Furthermore, the lengths of the double-blind cross-over phases are too short to capture changes in the CPCHILD as the primary outcome parameter. They may not even be long enough to document even subtle changes of dystonia at group level, because comparing DBS effects for a maximum of 24 h in the chronic state may not be a reliable measure for efficacy. In children who improve, there may not be any effects after turning off DBS for several days or even weeks [34]. Conversely, some children may even adapt to stimulation-even in the absence of an obvious effect on dystonia- leading to deterioration when DBS is suddenly switched off. Therefore, unlike other trials investigating the effects of DBS on dystonia in adults, we consciously decided to choose a short observational period to switch the generator off due to ethical considerations in the treatment of children as we want to protect these children from distracting deterioration of movements.

STIM-CP primarily serves as a pilot study to estimate the effect size that can be used for larger multicenter trials in the future. We also expect direct findings to improve treatment of DBS in children with acquired dystonia by generating knowledge about effects on motor as well as on and non-motor symptoms.

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Authors´ Contributions

Anne Koy and Lars Timmermann developed the study design and wrote the first draft of the manuscript. Martin Hellmich wrote the statistical analysis plan. Andrea A Kühn, Anne van Riesen, Julius Huebl, Rudolf Korinthenberg, Volker A Coenen, Joachim K Krauss, Andreas Wloch, Delia Lorenz, Martin Häussler, Alfons Schnitzler, Jan Vesper, Francois Alesch, Walter Lehmacher, Joerg Mueller, Guntram Borck, Karsten Witt, Tobias Bäumer, Steffen Berweck, Sebastian Schröder, Jürgen Voges, Reinhild Prinz-Langenohl, Veerle Visser-Vandewalle, and the STIM-CP investigators (Gerd-Helge Schneider, Svetlana Grünwald, Hans Hartmann, Joachim Runge, Christoph Schrader, Lars Wojtecki, Annette Horn, Vera Tadic, Volker Tronnier, Imke Galazky) made substantial contributions to the conception and design and had 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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Competing Interests

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Lars Timmermann received payments as a consultant for Medtronic Inc, Boston Scientific, SAPIENS, GE Medical, UCB Schwarz Pharma, Archimedes Pharma. L.T. received honoraria as a speaker on symposia sponsored by Zambon Pharma, TEVA Pharma, Medas Pharma, UCB Schwarz Pharma, Desitin Pharma, GlaxoSmithKline, Orion Pharma, Medtronic, Boston Scientific, Abbvie, GE Medical, Archimedes, Bayer, ProsStrakan Pharma. The institution of L.T., not L.T. personally received funding by the German Research Foundation, the German Ministry of Education and Research, Hoffnungsbaum e.V., NBIA Disorders Society USA, Köln Fortune, Medtronic, Deutsche Parkinson Vereinigung. Archimedes Pharma, Abott, Bayer, UCB, Zur Rose Pharma, TEVA. Neither L.T. nor any member of his family holds stocks, stock options, patents or financial interests in any of the above mentioned companies or their competitors.

Tobias Bäumer received honaria form Merz Pharmaceuticals, Ipsen Pharma and Allergan. He served on the scientific advisory board for Merz Pharmaceuticals.

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Joachim K Krauss is a consultant to Medtronic and Boston Scientific. He received honoraria for speaking from ST. Jude.

Andrea A Kühn is a consultant to Boston Scientific. She received honoraria for speaking from Medtronic, Boston Scientific and St. Jude Medical.

Annette Horn, Anne van Riesen, Andreas Wloch, Christoph Schrader, Delia Lorenz, Guntram Borck, Gerd-Helge Schneider, Hans Hartmann, Imke Galazky, Julius Huebl, Joachim Runge, Katharina Faust, Lars Wojtecki, Martin Häussler, Walter Lehmacher, Rudolf Korinthenberg, Steffen Berweck, Volker A Coenen, Vera Tadic, Volker Tronnier declare, that they have no competing interests.

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