RESEARCH ARTICLE

Effects of Deep Brain Stimulation in Dyskinetic Cerebral Palsy: A Meta-analysis

Anne Koy, MD,[1,2*] Martin Hellmich, PhD,[3] K. Amande M. Pauls, MD, PhD,[1] Warren Marks, MD,[4] Jean-Pierre Lin, MB ChB, MRCP (UK), PhD,[5] Oliver Fricke, MD,[6] Lars Timmermann, MD[1*]

[1]*Department of Neurology, University Hospital Cologne, Germany;*
[2]*Department of General Pediatrics and Neonatology, University Children's Hospital Düsseldorf, Germany;*
[3]*Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Germany;*
[4]*Department of Pediatric Neurology, Cook Children's Medical Center, Fort Worth, Texas, United States of America;*
[5]*Complex Motor Disorders Service, Pediatric Neuroscience, Guy's & St Thomas' Hospitals Foundation Trust & King's College Hospital Foundation Trust, King's Health Partners, London, United Kingdom;*
[6]*Department of Pediatric Neurology, University Hospital, Cologne, Germany.*

ABSTRACT: Secondary dystonia encompasses a heterogeneous group with different etiologies. Cerebral palsy is the most common cause. Pharmacological treatment is often unsatisfactory. There are only limited data on the therapeutic outcomes of deep brain stimulation in dyskinetic cerebral palsy. The published literature regarding deep brain stimulation and secondary dystonia was reviewed in a meta-analysis to reevaluate the effect on cerebral palsy. The Burke-Fahn-Marsden Dystonia Rating Scale movement score was chosen as the primary outcome measure. Outcome over time was evaluated and summarized by mixed-model repeated-measures analysis, paired Student *t* test, and Pearson's correlation coefficient. Twenty articles comprising 68 patients with cerebral palsy undergoing deep brain stimulation assessed by the Burke-Fahn-Marsden Dystonia Rating Scale were identified. Most articles were case reports reflecting great variability in the score and duration of follow-up. The mean Burke-Fahn-Marsden Dystonia Rating Scale movement score was 64.94 ± 25.40 preoperatively and dropped to 50.5 ± 26.77 postoperatively, with a mean improvement of 23.6% ($P < .001$) at a median follow-up of 12 months. The mean Burke-Fahn-Marsden Dystonia Rating Scale disability score was 18.54 ± 6.15 preoperatively and 16.83 ± 6.42 postoperatively, with a mean improvement of 9.2% ($P < .001$). There was a significant negative correlation between severity of dystonia and clinical outcome ($P < .05$). Deep brain stimulation can be an effective treatment option for dyskinetic cerebral palsy. In view of the heterogeneous data, a prospective study with a large cohort of patients in a standardized setting with a multidisciplinary approach would be helpful in further evaluating the role of deep brain stimulation in cerebral palsy.

Key Words: meta-analysis; deep brain stimulation; dyskinetic cerebral palsy

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Dr. Anne Koy, Department of Neurology, University of Cologne, Kerpener Strasse 62, 50924 Cologne, Germany; anne.koy@uk-koeln.de Correspondence to: Prof. Dr. Lars Timmermann, Department of Neurology, University of Cologne, Kerpener Strasse 62, 50924 Cologne, Germany; lars.timmermann@uk-koeln.de

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Cerebral palsy (CP) is the most common nongenetic cause of secondary dystonia, with an incidence of 2–3 per 1000 live births.[1,2] It is an umbrella term for a variety of symptoms caused by damage to the immature brain. The etiology is broad.[3,4] About 10%–15% of patients with CP develop a dyskinetic movement disorder,[5] although it is likely that this figure is an underestimate because of a failure to use operational definitions of spasticity and dystonia.[6] Although cerebral injury is nonprogressive, the involuntary movements typically start during early infancy and may be slowly progressive until adulthood.[1] Affected patients are frequently severely disabled in their motor function, whereas cognitive function is normal.

Pharmacological treatment is often unsatisfactory, or side effects are dose-limiting factors.[7] In patients with primary generalized dystonia, deep brain stimulation (DBS) of the globus pallidus internus (GPi) has been shown to be an effective and safe treatment.[8–13] During the last decade, several case reports and case series have been published about the therapeutic outcome of DBS in patients with dyskinetic CP reporting varying results.[14–36] The French SPIDY group led by Vidailhet performed the only prospective multicenter study, which included 13 patients with dystonia-choreathetosis CP.[16] Overall, GPi-DBS has been reported to improve dyskinetic CP in some patients, especially in young individuals, whereas others have shown no effect.

In view of the small numbers of patients, the substantial variability in the responsiveness to DBS, and the considerable clinical heterogeneity of patients with secondary dystonia, we investigated the effects of DBS on patients with dyskinetic CP in a meta-analysis of published patient data.

The aim was to assess the average response to DBS in these patients and to isolate outcome predictors in a larger cohort.

Materials and Methods

The PubMed database was searched for articles describing DBS for CP. The following search terms were used: "deep brain stimulation" and "secondary dystonia" or "cerebral palsy" (Supplementary Fig. 1). All articles were reviewed for pertinent patient data. Information on etiology of dystonia, age at operation, target of operation, duration of follow-up, stimulation parameters, adverse events, and outcome measures was obtained. Only articles written in English were reviewed, and only publications reporting individual clinical outcome data were included in the statistical analysis. Patients with other causes of secondary dystonia, such as metabolic or neurodegenerative diseases, were excluded.

Assessing the Outcome of DBS

The clinical outcome after DBS was most commonly assessed by the Burke-Fahn-Marsden Dystonia Rating Scale Movement (BFMDRS-M) and Disability (BFMDRS-D) score.[37] In some reports the Barry Albright Dystonia Rating Scale (BADRS),[38] the Unified Dystonia Rating Scale (UDRS),[39] or the Gross Motor Function Measure (GMFM)[40] were applied.

Meta-analysis

The data retrieved from individual case reports and small case series were pooled. The BFMDRS-M was chosen as the primary outcome measure. The scores of the BFMDRS at different follow-up times postoperatively were compared with the scores assessed before surgery. Four time categories were chosen (0 [baseline], 0 to $\leq$6, $>$6 to $\leq$12, and $>$12 months), and the mean scores were summarized accordingly for comparison. Outcomes over time were evaluated and summarized by mixed-model repeated-measures (MMRM) analysis (random intercept and slope, unstructured variance–covariance matrix), paired Student t tests and Pearson's correlation coefficients.

A subgroup analysis for the different entities for CP and the percentage improvement in the BFMDRS-M postoperatively was performed to reduce the substantial variability of clinical outcomes.

Changes in the BFMDRS were also given in percentages from baseline, as some authors did not provide the absolute score. Data distributions were summarized by mean, standard deviation, median, and range. Aggregated data from case series were weighted by sample size. $P \leq .05$ was deemed statistically significant. All statistical analyses and graphics were performed using SPSS Statistics 20.

Results

The analysis included all patients with a dyskinetic movement disorder associated with CP who had undergone DBS and whose clinical outcome was assessed by the BFMDRS-M.

The original database search revealed 261 articles. After selecting only those reports that included patients with CP as the exclusive cause of abnormal movements, 30 eligible articles were identified. Three articles had to be excluded because rating of the dystonic movements did not use the BFMDRS.[20,22,27] Five articles were excluded because they did not contain exact information on the number of patients affected by CP among others with secondary dystonia or because the BFMDRS could not clearly be assigned to individual patients in a mixed case series.[11,29,41–43] Two articles reported on the same patient in a different context (references [26] and [44], personal communication). The remaining 20 articles comprised either case reports or

TABLE 1. Overview of all patients with dyskinetic cerebral palsy after deep brain stimulation assessed by the BFMDRS-M included in the meta-analysis

Author, year	Pat. ID	Reference	Number of patients	Adverse events
Vercueil L, 2001	3	33	3	
Tronnier VM, 2000	4	23	1	
Krauss JK, 2003	5	14	4	Lead fracture (n = 1)
Zorzi G, 2005	6	24	1	
Zhang J, 2006	7	17	1	Lead fracture, lethargy (n = 1)
Vidailhet M, 2009	8	16	13	Worsening of dystonia (n = 4), deterioration after 1 year/cervical mylopathy (n = 1), subclavicular pain (n = 1), stim. arrest/magnetic field (n = 1)
Constantoyannis C, 2009	9	25	1	
Katsakiori PF, 2009	10	26	3	
Marks WA, 2011	12	15	14	
Pretto TE, 2008	13	30	2	
Woehrle JC, 2009	14	31	1	
Krause M, 2004	15	32	1	
Sakas DE, 2010	17	28	1	
Petacchi E, 2009	18	36	1	
Kim JP, 2011	22	34	10	Dysarthria, hemiparesis (n = 3)
Starr AP, 2006	23	21	1	
Air EL, 2011	24	45	3	Infection (n = 1)
Gimeno H, 2012	25	18	5	
Susatia F, 2010	26	19	1	
Park HS, 2011	27	35	1	

The given patient identifications (Pat. ID) match those shown in Figures 1 and 2.

case series assessing a total of 68 patients with dyskinetic CP who underwent DBS (Table 1).

Targets of DBS

In 64 of the 68 patients, the target of DBS was the GPi. Sixty patients underwent bilateral GPi surgery,[14–16,18,19,23,24,26,28,30–32,34–36,45] 3 patients unilateral GPi surgery,[14,21,26] and 1 patient received unilateral GPi surgery with additional stimulation of the contralateral subthalamic nucleus (STN).[17] One patient received unilateral stimulation of the nucleus ventralis oralis anterior (VOA/VLa).[25] In 3 patients the DBS target was the posterior portion of the ventral lateral nucleus of the thalamus (VIM/VLp), whereas 1 patient received GPi after unsuccessful stimulation of the VLp.[33] Six patients received bilateral GPi stimulation and also unilateral thalamotomy[34] (Supplementary Fig. 1).

Clinical Outcomes

In total, 64 patients were rated by the absolute BFMDRS-M score, whereas in 4 patients the change in BFMDRS was only given as percentage change from baseline.[33,36] The mean age at operation was 25.3 ± 11.3 years (range, 5–46 years). The outcome assessment was recorded at a median follow-up of 12 months (25th–75th percentiles: 6–24 months). The mean BFMDRS-M was 64.94 ± 25.40 preoperatively and 50.5 ± 26.77 postoperatively. This corresponds to an overall improvement of 23.6% ($P < .001$; Fig. 1).

As the duration of follow-up was variable, the scores assessed at different times were summarized over relevant time windows. Note that most studies only reported 1 postoperative BFMDRS of an individual patient; therefore, most of the patients in the 3 postoperative time categories (0 to ≤6, >6 to ≤12, and >12 months) were different. The mean BFMDRS-M assessed during the first 6 months after surgery was 56.62 ± 26.06, with a mean percentage improvement of 21.7% (n = 45; $P < .001$). Patients assessed between 6 and 12 months after surgery showed a mean BFMDRS-M of 49.19 ± 27.54 (25.2%; n = 38; $P < .001$). The mean BFMDRS-M after 12 months was 43.76 ± 14.65 (26.3%; n = 22; $P < .001$; Supplementary Fig. 2A).

The BFMDRS-D was assessed in 60 patients (absolute score; n = 56). The mean BFMDRS-D was 18.54 ± 6.15 preoperatively and 16.83 ± 6.42 postoperatively. The mean percentage improvement was 9.2% ($P < .001$; Fig. 2). The mean follow-up assessment during the first 6 months after surgery revealed a BFMDRS-D of 19.24 ± 5.16 (−7.4%; n = 39; $P < .001$), after 6–12 months a score of 16.74 ± 7.26 (6.8%; n = 36; $P < .05$), and after 12 months or longer a score of 15.52 ± 4.78 (10.6%; n = 20; $P = .001$; Supplementary Fig. 2B).

Patients who were not evaluated by the BFMDRS-M have been summarized but were excluded from the meta-analysis because of lack of comparability in terms of outcome: 1 patient rated by the BADRS with an improvement of 22%, 1 patient evaluated by the BADRS preoperatively (score 25) and by the BFMDRS postoperatively (score 76.5),[45] and 7 patients who were evaluated only by clinical assessment, without standardized rating scales. 3 patients with bilateral STN stimulation showed a slight decrease in muscle tone.[17] In 4 patients, 1 with unilateral thalamic- and 3 with bilateral GPi stimulation, a reduction in hyperkinetic movements was observed.[20,22,27] Coubes et al reported an overall improvement in the BFMDRS of 44% in a cohort of 17 patients with secondary dystonia, including 8 CP patients.[11] Legros et al assessed a median improvement of 26% in a mixed series of 5 patients affected by CP or pantotenate kinase–associated neurodegeneration.[42]

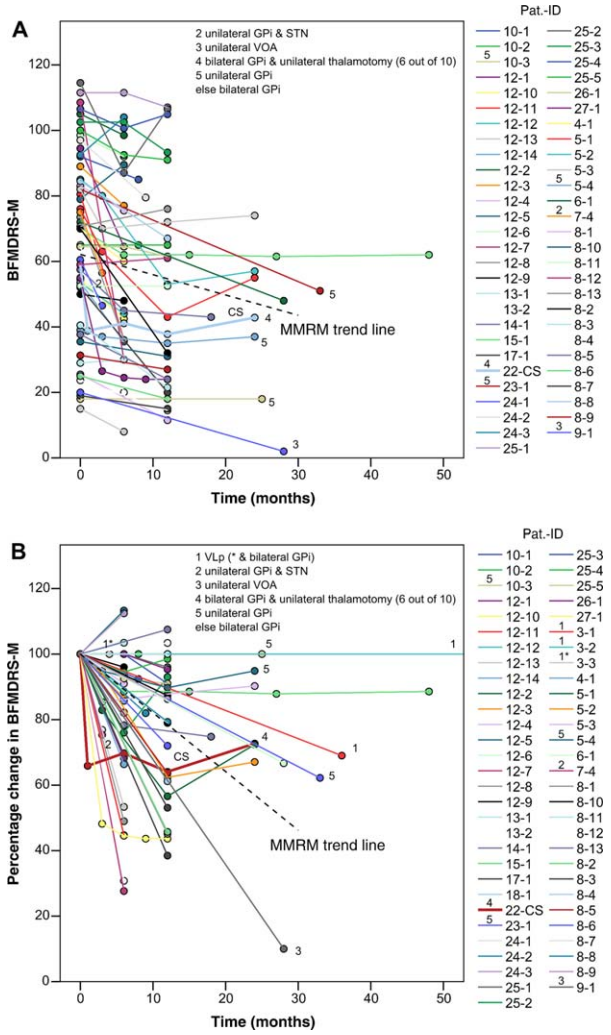

FIG. 1. Absolute (**A**) and percentage (**B**) changes in the BFMDRS-M of single patients or case series (CS) from baseline to the last follow-up ($P < .001$) are represented by colored dots. A trend line was fitted by MMRM. The single cases or case series are marked according to the target of DBS (no marking for bilateral GPi, 1 = VLp, 2 = unilateral GPi plus unilateral STN, 3 = unilateral VOA, 4 = bilateral GPi plus unilateral thalamotomy, 5 = unilateral GPi).

Quality of Life

Of the total of 20 studies, 4 provided quality-of-life data.[16,18,30,34] Two authors used the 36-item short form (SF-36) general health survey questionnaire.[46] Vidailhet et al reported about improvements in the subscores for body pain and mental health.[16] Kim et al found improvements in physical functioning, body pain, social functioning, and mental health in 10 CP patients after DBS, 6 of whom also received unilateral thalamotomy.[34] Pretto et al found improvement in the EuroQoL in 10 patients of a mixed case series of 13 patients including 3 patients with CP.[30,47] Gimeno et al assessed quality of life in 5 severely disabled CP patients after GPi-DBS using the Caregiver Priorities and Child Health Index of Life with Disabilities Questionnaire.[18,48] Three of the patients showed significant improvement 12 months after DBS. A functional assessment was also performed using the Canadian Occupational Performance Measure (COPM).[49] All 5 patients revealed clinically significant improvement in COPM performance, and 4 attained improvements in COPM satisfaction.[18] Krauss et al reported on 4 CP patients after DBS. Two of them felt marked improvement of symptoms after DBS surgery on a patient self-rating score.[14]

However, although the available data suggest improvement in quality of life after GPi-DBS, only a few studies have addressed this, and the heterogeneity of measures used prohibits further meta-analysis.

Outcome Predictors

We found no correlation between age at surgery (as a proxy for disease duration) and clinical outcome assessed

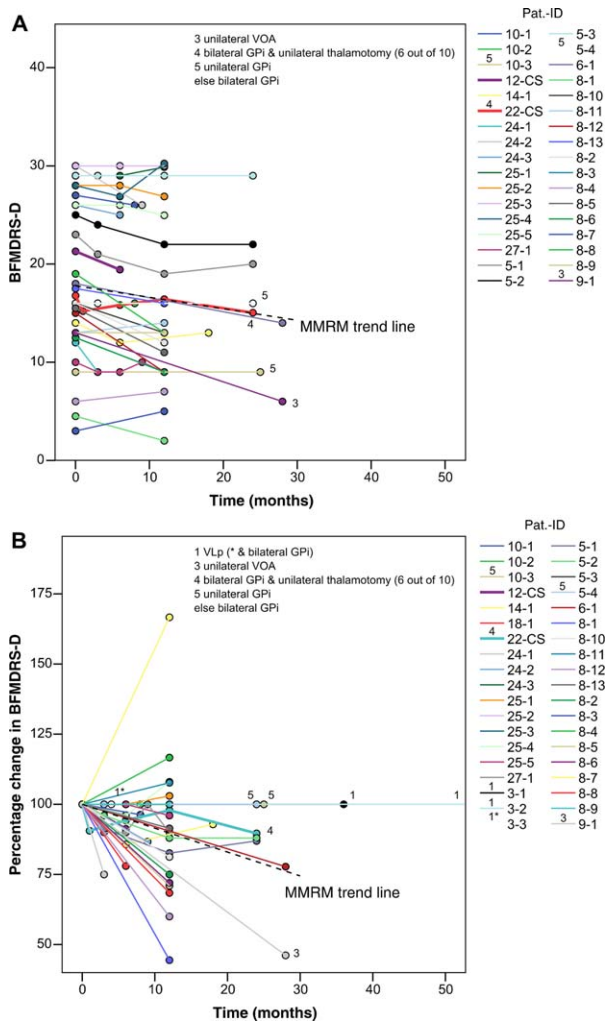

FIG. 2. Absolute (**A**) and percentage (**B**) changes in the BFMDRS-D of single patients or case series (CS) from baseline to the last follow-up ($P < .001$) are represented by colored dots. A trend line was fitted by MMRM. The single cases or case series are marked according to the target of DBS (no marking for bilateral GPi, 1 = VLp, 2 = unilateral GPi plus unilateral STN, 3 = unilateral VOA, 4 = bilateral GPi plus unilateral thalamotomy, 5 = unilateral GPi).

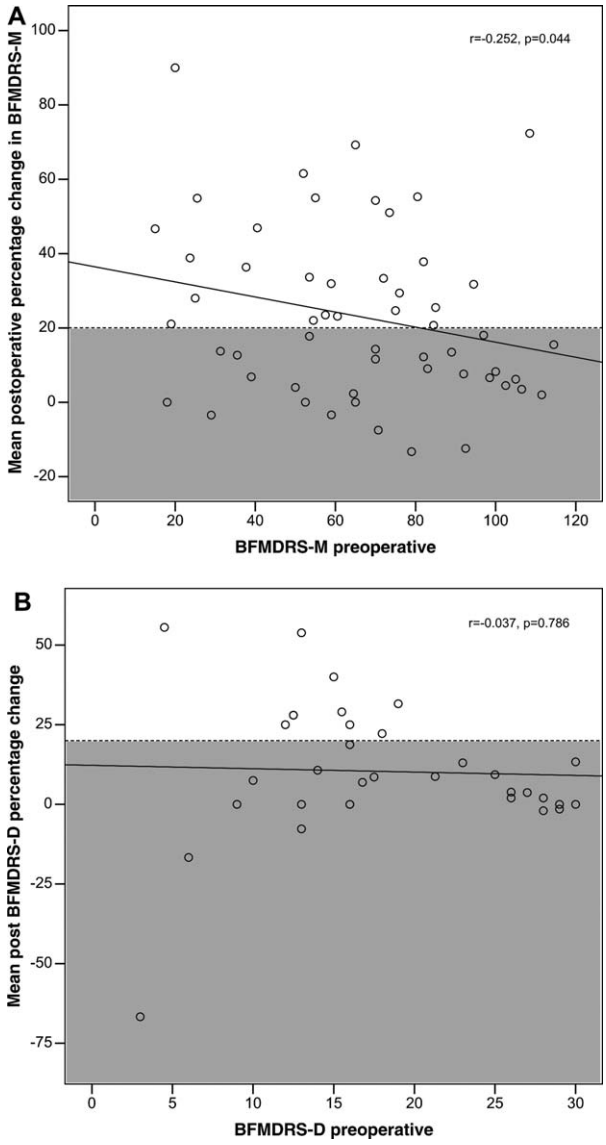

FIG. 3. Negative correlation between the severity of dystonia and the percentage improvement after deep brain stimulation. **A:** *x* axis, BFMDRS-M preoperatively; *y* axis, percentage change in the BFMDRS-M postoperatively. **B:** *x* axis, BFMDRS-D preoperatively; *y* axis, percentage change in the BFMDRS-D postoperatively.

by the BFMDRS (age vs mean percentage change of BFMDRS-M, $r = -0.070$; $P = .570$; age vs mean percentage change of BFMDRS-D, $r = -0.146$; $P = .267$).

The preoperative BFMDRS-M showed a significant negative correlation with the postoperative percentage improvement ($r = -0.252$; $P<.05$). This implies that the more severe dystonia was before DBS, the smaller was the postoperative percentage of improvement. There was no correlation between the BFMDRS-D preoperatively and the percentage improvement of the BFMDRS-D postoperatively ($r = -0.037$; $P = .786$; Fig. 3).

For subgroup analyses, please see Supplementary Material (supplementary text and Supplementary Tables 1 and 2).

Stimulation Settings and Adverse Events

Information regarding stimulation settings was incomplete. Some studies gave mean values for case series including patients with secondary dystonia of different etiologies. The following mean stimulation parameters only included data clearly allocated to CP patients investigated in this meta-analysis (n = 46). The mean amplitude was 3.2 ± 1.0 V (range, 0.8–6.5 V), the mean frequency was 111.8 ± 40.1 Hz (range, 30–180 Hz), and the mean pulse width was 167.6 ± 56.6 μs (range, 90–450 μs). No specific parameter settings were specifically associated with improvement in dystonia (percentage improvement of BFMDRS-M vs amplitude, $r = -0.271$, $P = .069$; percentage improvement of BFMDRS-M vs frequency, $r = 0.077$, $P = .612$; percentage improvement of BFMDRS-M vs pulse width, $r = 0.152$, $P = .315$).

Only a very few studies reported adverse events. Most adverse events were summarized for larger case series that included patients with secondary dystonia of various etiologies. Table 1 lists adverse events after DBS that could clearly be assigned to individual CP patients.[14,16,17,34,45]

Discussion

Our meta-analysis of individual patient data showed a moderate but significant improvement in the BFMDRS-M (23.6%) and BFMDRS-D (9.2%) in patients with dyskinetic CP after DBS surgery. The published results were very variable, and the overall response was far less dramatic than has been reported in patients with primary generalized dystonia.[8–10,50,51]

Factors Influencing the Outcome of the Analysis

Several factors seem likely to have influenced the outcome. Most of the publications consisted of case reports or small case series not exceeding 4 or 5 patients, apart from 3 larger series, whereas in 1 of the case series, 6 patients also received unilateral thalamotomy.[15,16,34]

Furthermore, the technical procedures differed among the various reports. In most of the cases, the GPi was chosen as the primary target for DBS. Some studies reported different localizations such as the STN or thalamus with varying results.[17,22,26,33] The difficulty of the exact electrode placement because of the often altered anatomy of injured basal ganglia might also account for the heterogeneous results. Perioperative microrecordings were not systematically performed, which might have been because many of the patients were operated on under general anesthesia. Vidailhet et al reported that the postoperative location of the electrodes in CP patients was more variable

than reported in patients with primary dystonia, most likely because of altered cerebral anatomy.[16]

Varying outcome results might also be attributed to the individual experience of the DBS centers. Some clinics that perform more than 100 DBS implantations per year, including many pediatric and adolescent patients with dystonic movement disorders, are more experienced, especially concerning the technical procedures.[43,45]

There is also limited information on DBS settings. Each patient was individually adjusted with different parameters. The clinical courses were therefore difficult to compare in terms of standardized settings.

CP patients are very heterogeneous in terms of etiology and the extent of brain damage. Not all studies provided sufficient information on these issues. The 2 larger subgroups of patients with CP from hypoxia/ischemia or prematurity showed significant improvement in the postoperative BFMDRS-M, which is comparable to the mean improvement extracted by our meta-analysis. In view of the very small number of patients in the other subgroups, no conclusions can be drawn.

The postoperative improvement in the BFMDRS appeared to be maintained in the long-term follow-up, with increasing variability. However, long-term follow-up data were only available from a few single cases and case series comprising a total of 20 patients.[14,21,24–26,31,32,34] It is of note, that 6 of them also received unilateral thalamotomy.[34] There also may be a publication bias toward favorable outcomes, and results have to be interpreted with caution.

The duration of disease and the severity of symptoms were also variable among CP patients. They often suffered from concomitant spasticity with progressive joint contracture. Restricted mobility or abnormal postures induced by sustained contractions of muscles can lead to fixed skeletal deformations such as premature degenerative spine disorders.[52] Therefore, Vidailhet et al concluded from their series of CP patients that irreversible changes cannot be influenced by DBS, whereas it seems likely that patients with only little spasticity and more phasic movements than tonic posturing will benefit more from DBS.[16]

The age of CP patients at DBS surgery was very variable. Isaias et al and Andrews et al showed that a shorter duration of symptoms in patients with primary idiopathic dystonia was associated with a higher percentage of improvement after DBS surgery.[53,54] Other studies suggested that the younger the patients, the better was the response to DBS.[15] However, our meta-analysis did not show any correlation between age and clinical outcome, which might be attributable to the highly variable extent of disability of each individual patient in this heterogeneous group. Indeed, there was a significant negative correlation between severity of dystonia and clinical outcome. This implies that the less affected the patients, the higher the percentage improvement after DBS. Patients with improvement in the BFMDRS of less than 20% are often referred to as "nonresponders." Based on our meta-analysis, it might be speculated that patients with a preoperative BFMDRS-M more than 85 have a very high risk of ending up as DBS nonresponders. But this should be interpreted with caution given the variability of symptoms and outcomes.

The BFMDRS is still the most commonly used rating scale to evaluate the effect of DBS. In patients with mixed movement disorders, this rating scale does not fully cover motor impairment, as it is insensitive to individual limb components or hyperkinetic movements.[15,16,55,56] Generally, the sole use of impairment measures does not seem to sufficiently encompass the effect of DBS on the complex disability of CP patients. Only a few studies have addressed this so far. Some clearly demonstrated that quality of life, function, pain, and caregiver burden can be considerably improved after DBS—even without clinically measurable changes in dystonia severity.[16,18,57] Most of these patients perceive their improvement after DBS in quite a different way than is reflected by common clinical rating scales, and small changes in function or mobility seem to bring essential benefit for these severely handicapped patients.[14,23,45] Therefore, quality-of-life assessments as well as goal-setting scores with subjective judgments by the patients or carers like the COPM seem to capture meaningful changes more thoroughly.[18,57]

Complications and Adverse Events

Interestingly, hardly any major surgical complications or permanent side effects associated with DBS were reported. Kaminska et al referred to a low complication rate in a large cohort of pediatric and adolescent patients, whereas Air et al did point out a significantly increased risk of device complications and hardware infections among children.[45,58]

Limitations and Outlook of the Study

The limitations of this meta-analysis have to be critically considered, and data have to be interpreted with caution. However, we present the first analysis of a large cohort and corroborate the findings of single cases and small case series. We interpret the data of our study in the way that DBS is a serious option for patients with dyskinetic CP with hope of moderate improvement in motor function as well as in quality of life. Patients, caregivers, and treating physicians have to be clear that the clinical benefit is less dramatic than in idiopathic dystonia. This is in accordance with the conclusions of the only prospective, multicenter study to date.[16] So far, individual outcomes for CP patients after DBS cannot be predicted. Therefore, further research is needed to elucidate whether differences in outcomes are a result of patient characteristics such as

duration of disease, phenomenology of symptoms, and extent of brain damage, or whether they also depend on technical issues, for example, the site of implantation, or on other, yet-unknown factors.

Improvement in quality of life with participation in daily activities seems to be the key issue for CP patients undergoing DBS and should be thoroughly examined. A long-term study with a large cohort of CP patients in a standardized setting with a multidimensional approach is needed to further evaluate the role of DBS in the therapy of dyskinetic CP patients.

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