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Thalamic Deep Brain Stimulation for Acquired Dystonia in Children and Young Adults: A Phase I Clinical Trial

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Abstract

Objective: To evaluate feasibility, preliminary efficacy and safety of bilateral ventralis oralis posterior/ventralis intermedius (Vop/Vim) deep brain stimulation (DBS) for the treatment of acquired dystonia in children and young adults. Pallidal DBS is efficacious for severe, medication refractory isolated dystonia, providing 50–60% long-term improvement. Unfortunately, pallidal stimulation response rates in acquired dystonia are modest and unpredictable with frequent non-responders. Acquired dystonia, most commonly caused by cerebral palsy, is more common in pediatric populations than isolated dystonia and more recalcitrant to standard treatments. Given the limitations of pallidal DBS in acquired dystonia, there is a need to explore alternative brain targets. Preliminary evidence suggests that thalamic stimulation may be efficacious for acquired dystonia.

Materials and methods: Four participants, three with perinatal brain injuries and one with postencephalitic symptomatic dystonia, underwent bilateral Vop/Vim DBS and bimonthly evaluations for 12 months. The primary efficacy outcome was the change in Burke-Fahn-Marsden (BFMDRS) and Barry-Albright (BADS) Dystonia Rating Scales at 12 months. Video documentation was used for blinded ratings. Secondary outcomes included evaluation of spasticity (Modified Ashworth Scale), quality of life (PedsQL™, Modified Unified Parkinson Disease

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Analysis and interpretation of data: MS, ARV, IOB, SW, PAS, JLO

Drafting of the article: MS, ARV

Statistical analysis: MS

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Administrative/technical/material support: ACV

Study supervision: MS, ARV

Rating Scale Part II, UPDRS-II) and neuropsychological assessments. Adverse events were monitored for safety.

Results: All participants tolerated the procedure well and there were no safety concerns or serious adverse events. There was an average improvement of 21.5% in BFMDRS motor subscale, but only 1.6% in BADS. Following blinded video review, dystonia severity ratings were even more modest. Secondary outcomes were however more encouraging, with the BFMDRS disability subscale improving by 15.7%, the PedsQL™ total score by 27%, and the modified UPDRS part II by 19.3%. Neuropsychological assessments were unchanged one year after surgery.

Discussion: Bilateral thalamic neuromodulation by DBS for severe, refractory acquired dystonia was well tolerated. Primary and secondary outcomes showed highly variable treatment effect sizes comparable to pallidal stimulation in this population. As previously described, improvements in quality of life and disability were not reflected in dystonia severity scales, suggesting a need for the development of scales specifically for acquired dystonia. (Clinical trial number: NCT03078816)

INTRODUCTION

Dystonia is a movement disorder seen in both children and adults that is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both[1]. Acquired dystonia, or dystonia resulting from damage to the nervous system or degenerative processes, especially secondary to perinatal brain injuries resulting in cerebral palsy, is far more common in pediatric populations than isolated dystonia, and notoriously more recalcitrant to standard pharmacologic and surgical treatments[2, 3].

Pallidal deep brain stimulation (DBS) is highly efficacious for severe, medication refractory, generalized, segmental and some focal isolated dystonia forms[4], providing long-term symptom control and improved function with average improvements ranging from 50 to 60%, depending on various factors[5]. Unfortunately, the response rates of pallidal stimulation in acquired dystonia are only modest and unpredictable with a mean reduction of dystonia symptoms of only ~23% and frequent non-responder cases[6].

Given the limitations of pallidal DBS in acquired dystonia, alternative brain targets are being explored, and the thalamus may be an attractive candidate.

Historically, acquired dystonia patients have shown improvement following thalamotomy[7] although the procedure was eventually abandoned due to a tendency for loss of efficacy over time[8] and perceived high prevalence of side effects and complications, especially when performed bilaterally[9]. Thalamic deep brain stimulation has been evaluated for dystonia in a few small open label studies, mostly in conjunction with pallidal stimulation[10–12]. By targeting the border of the ventralis oralis posterior (Vop) and ventralis intermedius (Vim) nucleus, the stimulation might strategically affect inputs from both the pallidum and the cerebellum leading to a more effective treatment than pallidum stimulation alone, especially since acquired dystonia often is multifactorial and cerebellar pathways may be involved in its pathogenesis[13].

In this study, we carefully explored the effect of thalamic Vop/Vim stimulation in a group of patients with acquired dystonia, caused mainly from perinatal brain injuries, with the primary aim of evaluating feasibility and safety as well as a preliminary look at efficacy, and to set the stage for future, larger scale clinical trials.

METHODS

This was a single-institution, open-label, phase I clinical trial of Vop/Vim DBS in children and young adults with severe acquired dystonia despite appropriate conventional treatment. The study was approved by the Institutional Review Board at University of California, San Francisco (UCSF) and Food and Drug Administration under an Investigational Device Exemption (IDE G162033), clinical trial number: NCT03078816.

Study Participants

Participants were recruited from the UCSF Movement Disorders and Neuromodulation Center and the Pediatric Neurology Clinics at UCSF Benioff Children's Hospitals in San Francisco and Oakland, California. Participants were eligible if they were 7–25 years of age by day of surgery and had confirmed acquired dystonia diagnoses (for example, a clear history of hypoxic-ischemic brain injury preceding dystonic symptoms) with or without MRI abnormalities. To qualify, patients' dystonia had to have been present for at least six months and have been severe enough to warrant surgical intervention. Enrollment in the study also required verification of relatively intact thalamic anatomy for two years prior to surgery. Exclusion criteria included pregnancy and/or breast feeding, major comorbidities that would increase surgical risk, active infection at time of surgery, requirement of diathermy, electroconvulsive therapy or transcranial magnetic stimulation, presence of previously implanted neurostimulators, pacemakers, defibrillators or metallic head implants, history of exposure to neuroleptic agents, dystonia caused by known genetic mutations, severe cognitive impairment or dementia (estimated nonverbal IQ < 70), and uncontrolled depression. For one participant, written informed consent and assent was obtained with help from a medical Spanish interpreter. For the three participants who were less than 18 years of age, written or verbal assent was also obtained. A Data and Safety Monitoring Board, which included a movement disorders neurologist and neurosurgeon at University of California, San Francisco not otherwise involved in the study, was arranged, meeting biannually and *ad hoc* to review trial progress. After completion of endpoint evaluation and prior to study separation, all participants with implants were provided ample opportunity to discuss pros and cons of continuing with stimulation, stopping stimulation but leaving DBS system in place, or stopping stimulation and removing part or all of the DBS system. Each of the four participants elected to continue DBS stimulation, and two chose to continue being followed clinically at our Center. Figure 1 illustrates the flow of events for all participants.

Outcome Assessments

Baseline assessments were performed 60 days prior to DBS surgery, and final endpoint assessments were performed following 12 months of continuous thalamic stimulation. Burke-Fahn-Marsden (BFMDRS) and Barry Albright Dystonia (BADS) rating scales were performed by the treating movement disorder neurologists (ARV and MS) before surgery

and were repeated bimonthly over the course of the study. These severity ratings were tested for reliability by a blinded investigator (IOB), who independently repeated these assessments through video recordings without knowledge of prior ratings, DBS status, or time-point in the study. Spasticity was evaluated as well, according to bimonthly administrations of the Modified Ashworth Scale. The PedsQL™ and a modified version of the Unified Parkinson's Disease Rating Scale Part II (previously used and modified for use in Panthothene Kinase Associated Neurodegeneration)[14] were administered to the participants and caregivers at six and 12 months to assess the effect of DBS on quality of life.

Additionally, each participant underwent baseline and postoperative neuropsychological evaluations by trained neuropsychologists (CAR, CP). The battery included measures of intellectual abilities (Kaufman Brief Intelligence Test 2nd Edition[15], KBIT-2, Crystallized Scale & Fluid Scale), behaviors and emotion (Behavior Assessment System for Children, 3rd Edition, BASC-3[16], SRP-A (self-report) & PRS-A (parent rating)), psychiatric symptoms (DSM-5 Mood Screener[17], self- and parent-rated), and speech (diadochokinetic syllables). Standardized normative data was used to transform raw scores into standard scores. All patients had difficulties with expressive language, and most relied on eye gaze communication, head nods or other gestures to communicate responses to questions. Given the participants' differing visual-motor communication and fine motor control impairments, the psychometric testing was customized for each participant. Not all individuals were able to complete all measures due to motor difficulties, language impairment, and fatigue resulting from the effort and time required to communicate their answers.

Deep Brain Stimulation Surgery

Participants underwent implantation of bilateral DBS leads (Medtronic 3389 leads, Medtronic, Minneapolis, MN) in the Vop/Vim nuclei of the thalamus under general anesthesia using interventional MRI surgical guidance as described in previous publications from our center[18]. Bilateral Medtronic Activa single cell (SC) implantable pulse generators were implanted subcutaneously below the clavicle. The leads were implanted using a novel skull-mounted aiming device in conjunction with dedicated software (ClearPoint™ system), used within a 3T diagnostic MRI scanner (Philips Intera, 60-cm bore diameter) in a radiology suite, with the patient under general anesthesia and without neurophysiologic testing. Details on this methodology have been previously published[18]. The Vop/Vim border within the thalamus was targeted approximately 10 mm lateral to the ipsilateral border of the third ventricle and 6 mm anterior to the posterior commissure at the level of the anterior commissure-posterior commissure plane. While it is difficult to visualize nuclear boundaries within the thalamus, we utilized Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) imaging, reformatted in the axial and coronal planes, to visualize the thalamocapsular border. We adjusted the lateral coordinate, as well as the exact lead trajectory, to ensure that the contact area would be located 2–3 mm medial to this border. Postoperative MRI was obtained in all participants and transferred to Framelink to document lead locations. The coronal and sagittal approach angles and lead entry and tip positions in anterior commissure-posterior commissure (AC-PC) coordinates are listed in Table 1. T1-weighted MRI images of lead location in all participants are shown in Figure 2. Following

the intervention, participants were transferred to the Pediatric Intensive Care Unit for 1–2 nights and then to the floor unit for post-operative care. Given that pediatric patients and wheelchair bound patients carry a high risk of infection, all participants received an enhanced post-operative antibiotic regimen of 48 hours of intravenous vancomycin and ceftriaxone, followed by 10 days of oral dicloxacillin. This antibiotic regimen has shown significantly reduced numbers of infections compared to historical studies in this population[19].

Stimulation Optimization

Stimulation was initiated approximately one month following implantation. During the first programming session, each of the four contacts were activated in a monopolar mode to perform a monopolar survey, with a single contact assigned to be the cathode and the internal pulse generator (IPG) as the anode. The pulse width and frequency were fixed at values typical for dystonia (pulse width 60 microseconds, frequency at 130 Hz), and the amplitude was increased by 0.5–1V increments, from 0 to 4–5V. At each amplitude, the participant was queried on stimulation related side effects and examined for changes in dystonic symptoms. Participants returned for post-operative programming and data collection visits bimonthly (except for Participant 4 who had visits only at 2, 10 and 12 months). DBS settings were only permitted to be changed every eight weeks to allow for settings to reach steady state and fully allow for evaluation of effectiveness by caregivers and patients. Any improvement in dystonia during DBS programming was noted. This programming paradigm was based on historical data of programming of GPi DBS in dystonia[20]. DBS stimulation settings at 12 months are listed in Table 1.

Data Analyses

Analysis of this Phase I clinical trial was designed to assess the safety of continuous thalamic stimulation and to estimate treatment effect size for future design of larger scale trials. The primary outcome of this analysis was variation in dystonia severity across the 12-month study period, as determined by differences in BFMDRS and BADS rating scales, while secondary outcomes included variation in spasticity, quality of life, and neuropsychological assessment. The non-parametric Wilcoxon matched-pairs signed-rank test was applied (2-tailed; alpha set at 0.05) to study differences between baseline and 12-month outcomes.

Adverse Events

Prior to study enrollment, participants and participants' legal representatives were informed of the potential risks of undergoing DBS surgery in a lesser studied brain target for this indication. During the trial, participants and representatives kept a log of stimulation related adverse events (AEs) and were interviewed in detail by the study team during every in-person evaluation for stimulation related and other adverse events. Participants with implants and their representatives understood their unequivocal right to separate from the study at any time and the fact that the study team could terminate their participation for medical or safety reasons.

RESULTS

Participant Demographics

Five prospective participants were screened, underwent comprehensive evaluations, and met inclusion criteria for enrollment. One declined further engagement prior to surgery, but the remaining four participants were eventually implanted and remained in the study for its duration. These four participants were comprised of two males and two females, with a mean (standard error) age of 14.5 years (2) and a mean dystonia duration of 13 years (2.6). Demographic and clinical information for these four participants are listed in Table 2. Briefly, Participant 1 developed spasticity and generalized dystonia following West Nile encephalitis at age 7. Participant 2 was born prematurely at 26 weeks after premature labor and low-lying placenta, and displayed delay in all early psychomotor milestones and subsequently spastic dystonic quadriparesis. He had a known grade 4 intraventricular hemorrhage with periventricular leukomalacia at birth. Participant 3 was born in cardiac arrest at week 37 via emergency cesarean section for cord prolapse and developed early spastic quadriparesis and generalized dystonia. Lastly, Participant 4 was born at 39 weeks following presumed birth asphyxia and neonatal seizures and developed a mixture of dystonia and spasticity (video). Details and images of T2-weighted preoperative MRI from all participants are shown in Figure 3.

Primary Outcomes

The mean baseline motor BFMDRS and BADS scores were 75.4 (standard error, 7.2) and 21.2 (1.4), respectively. The mean decrease in motor BFMDRS following 12 months of continuous thalamic stimulation was 14.7 (11.8) points and ranged from a 0.5-point increase to a 25-point decrease. This represented an average improvement of 21.5%. The total BADS score decreased by an average of 0.25 (3.2) points and ranged from a 2-point increase to a 3-point decrease, a 1.6% improvement. These differences were not statistically significant after application of the non-parametric Wilcoxon match-pairs signed-rank test (p-value of 0.14 for motor BFMDRS and 0.70 for BADS). In the blinded video review, there was an average decrease in motor BFMDRS of 0.33 (3) points (p-value=0.99), and an increase of 2 (1.7) points in BADS (p-value=0.31). Primary efficacy outcomes are displayed in Table 3.

Secondary Outcomes

All participants had upper and lower limb spasticity at baseline (average Modified Ashworth Scale score for upper limb of 1.9 and 1.7 for lower limb, Table 4). At 12 months, there was a non-significant average increase in spasticity in both upper and lower limbs (0.29 and 0.26-point increase in upper and lower limbs respectively, p-value=0.57 in both cases). Neither the participants, their caregivers, nor clinicians involved in the study considered the increase in spasticity demonstrated in the scales clinically relevant. Instead, all caregivers reported that the home physical therapists reported reduced tone and increased passive mobility compared to prior to surgery.

The BFMDRS disability subscale showed wide variability but improved by an average of 15.7% compared to baseline (range: 9.1% worsening to 53.8% improvement, p=0.23), and the PedsQLTM ™ improved an average of 27% (range: 0% to 54.8% improvement, p=0.09).

The Modified UPDRS-II was only available at 12 months for two participants and showed an improvement of 23.5% for one participant and of 15% in the other (Table 5).

Follow-up neuropsychological testing at 12–25 months postoperatively did not show clinically meaningful worsening in any domain, and findings remained stable overall (Supplementary Table).

Subjective and Functional Outcomes

Despite nonsignificant changes in rating scores observed, improved functionality and ability to perform daily skills were reported in all but one patient and participants reported qualitative improvements. For example, Participant 4, who suffered frequent falls prior to surgery, displayed no measurable changes in ambulatory status, but saw a significant reduction in frequency of falls, and even gained the ability to run. Because of these improvements, she had removal of restrictions on the playground, and she no longer required a helmet to keep her safe (video #2). Participant 2 no longer required restraint of his upper limbs to avoid self-harm from dystonic movements. Three participants exhibited improvements in sleep due to increased ability to turn over in bed, and caregivers reported improvement in transfers and gain of some independence with toileting.

Anecdotally, during postoperative neuropsychological evaluations, there was reported improvement in assessments of depression, anxiety and irritability, psychotic symptoms, and improved sleep in three participants. (Supplementary Table).

Safety Outcomes

All participants tolerated the procedure well and there were no safety concerns or serious adverse events. Some degree of anticipated mild stimulation-related temporary side effects was experienced by all participants, particularly during the initial programming monopolar review, where the neurostimulator was interrogated to determine maximum tolerable voltage. Each of these side effects, which included paresthesia of tongue and limbs, dysarthria and mouth pulling, transient increase in bothersome movements, and feelings of discomfort, were resolved by lowering the voltage. Additional unanticipated adverse effects included postoperative diarrhea likely related to the precautionary antibiotic course. One participant developed new speech difficulties, decreased energy, and unwillingness to assist with rolling over following stimulation changes at the 10-month visit (perceived by family as apathy). These side effects were initially attributed to a viral infection but resolved after lowering the voltage slightly.

DISCUSSION

This open-label phase I trial evaluating preliminary efficacy and safety of bilateral Vop/Vim thalamic DBS for severe acquired dystonia in four children and young adults showed feasibility, adequate tolerability and safety, and some encouraging preliminary results.

Thalamic stimulation presented no irreversible complications. Beyond the expected stimulation-induced side effects present during monopolar review and one episode of potential transient stimulation-induced apathy, there were no long term or permanent side

effects or complications. Notably, there were also no infections, which is the most common complication in this study population. There is uncertainty in the lead targeting with respect to the Vim/Vop boundary in the antero-posterior direction, given the inability to distinguish these nuclei anatomically at 3T. While microelectrode recording could have been used in principle to map the boundary between motor and sensory thalamus, this method is impractical in asleep patients implanted within an MR scanner. Postoperative imaging confirmed that leads were implanted within 1 mm (radial error) of the intended target.

Primary and secondary outcomes revealed highly variable effect sizes with unblinded severity ratings showing 21.5% improvement in BFMDS at 12 months, which is similar to previously reported outcomes of pallidal stimulation[21, 22]. Unsurprisingly, the participant with the shortest dystonia duration, who was also the youngest, saw the greatest improvement. She also was the most functional at baseline and had the least structural damage seen through MRI, both of which have been shown to be likely predictive factors of success rates for pallidal stimulation[21, 23, 24].

Acquired dystonia, especially secondary to perinatal injuries (commonly clinically referred to as cerebral palsy), represents one of the most common causes of dystonia in children and young adults. The overall reported prevalence of cerebral palsy in children aged 3–10 is 2.4 per 1,000 children, and movement disorders including dystonia, athetosis, and chorea are common manifestations[3, 12], affecting up to 15% of patients[25] and the surgical treatment of severe acquired dystonia in cerebral palsy remains an important challenge.

A 2013 metanalysis of pallidal DBS in acquired dystonia which included 19 unblinded studies showed an overall improvement of 23.6% in BFMDRS motor and of 9.2% in BFMDRS disability scores[6], with greater improvement seen among younger individuals. More recent studies confirm highly variable and often disappointing gross motor responses in other etiologies apart from isolated dystonia[26, 27] (including acquired, heredodegenerative and idiopathic dystonia), highlighting the need for alternative brain targets.

There is growing recognition that brain structures outside of the basal ganglia are involved in dystonia, and dystonia is now generally understood as a network disorder[13, 28]. Dysfunction of the cerebellum and related thalamocortical circuits can lead to dystonia, likely through dysfunctional interactions with the basal ganglia circuitry, and neuromodulation of such cerebellothalamic pathways may improve dystonic symptoms[13, 29]. In isolated dystonia, for example, targeting of the Vim is now considered to be an equivalent, or even superior approach to targeting GPi for the management of dystonic tremor, as well as for cases where tremor is the patient's most disabling symptom[30, 31]. In acquired dystonia, which is considered etiologically multifactorial and in which thalamocerebellar pathways are frequently affected[32], both cerebellar[33] and thalamic targets have been explored. Thalamic stimulation has been explored for the treatment of acquired dystonia and choreoathetosis in a handful of small heterogeneous studies, but mostly in combination with pallidal stimulation. Wolf *et al.* reported the results of concurrent pallidal and Vim stimulation among three adult patients with cerebral palsy, which displayed results equivalent to those of pallidal stimulation alone for all but one patient[12]. In a separate study, addition of Vop leads to pallidal DBS was effective in addressing complex movement disorders in two patients with

neuroacanthocytosis[34], and stimulation of the VOP itself improved severe trunk spasms in another patient with neuroacanthocytosis[35]. Addition of bilateral ventralis oralis anterior electrodes to pallidal DBS also brought marked improvements in a single participant with severe postanoxic dystonia and bilateral basal ganglia necrosis[36].

Specific targeting of the Vop and Vim according to electrophysiological perioperative data using stereo EEG depth electrodes in children with acquired and combined dystonia has led to improved outcomes in a novel approach to DBS target selection[11]. Stimulation of the combined Vop/Vim area, which has the potential to affect both pallidal and cerebellar inputs and provide a more efficient therapeutic option for this population, has not been previously studied in a rigorous manner.

Our study witnessed improvements to quality of life that were not captured by validated rating scales. These included an increased ability to turn over in bed, which in turn reportedly improved sleep quality, an improvement in transfers and toileting, greater weight bearing ability during walking, decreased reliance on physical restraints, and fewer falls during ambulation. Additionally, there was reported improvement in psychiatric symptoms (depression, anxiety, irritability, psychosis) in 3/4 participants, with the most functional participant showing the greatest benefits. Despite these reported improvements in quality of life and mood, unblinded BADS ratings and blinded video BFMDRS and BADS ratings did not show the same degree of improvement. This discrepancy has been noted in many other studies of DBS in cerebral palsy or other acquired dystonias[23, 37, 38]. Current gold-standard rating scales relied upon by movement disorder neurologists to assess severity and disability do not adequately capture many of the symptoms that may improve with DBS. As a result, symptomatic improvements such as those witnessed in our study may only be detected upon a careful review of systems[23]. The current dystonia rating scales also fail to adequately measure individual limb components and cannot account for spasticity and joint contractures, common features of mixed movement disorders in acquired dystonia[3, 23]. The differences found between our blinded and unblinded ratings are hence likely due to a combination of lower interrater reliability and sensitivity in children, differential observation time during in-person evaluations versus the shorter videotaped clips, and biased outcome ascertainment due to lack of blinding. These findings highlight the importance of performing adequate blinded evaluations in future trials, and as previously suggested[39, 40], the need to develop rating scales more suitable to acquired dystonia. Application of wearable technology, perhaps along with video analysis to quantify objective changes in complex movements, may provide a solution to this problem. Systems such as these, which would more easily quantify subtle symptoms, may prove to be a superior alternative to simply relying on adaptations of existing movement disorders scales developed specifically for isolated dystonia and adult onset movement disorders. Until such systems can be integrated, clinical studies of pediatric DBS should continue to rely on best-available measures including open-ended symptom reviews and quality of life measures to fully capture the benefits and pitfalls of DBS.

There is an unmet need for methods to reliably determine intellectual capacity and cognitive ability in patients with severe motor impairments. Attempts to circumvent this necessity by individualizing neuropsychological testing still brought significant challenges. We attribute

some of these challenges to oculomotor apraxia, which limited the utility of non-verbal cognitive assessments. There were also other difficulties in discerning which answer the participant intended to use due to limitations from dystonia, physical and mental fatigue, and differential life experiences relative to those typically experienced by children without significant motor impairment.

Our study represents one of only a few prospective studies of DBS involving children. Significant strengths of our study include the well-characterized preoperative and postoperative profiles of our cohort, use of validated outcome assessments, and inclusion of blinded video ratings. Limitations, however, include the small number of participants implanted and the etiological heterogeneity of those patients successfully recruited, despite the commonality of all four participants having suffered structural brain damage. However, even in cases where acquired dystonia could be limited to one cause, for example hypoxic-ischemic injury at birth, the distribution of brain damage will always vary between participants, making a homogeneous participant population nearly impossible.

CONCLUSION

Bilateral Vop/Vim thalamic neuromodulation by DBS is feasible, well tolerated and safe for severe acquired dystonia. While the measurement tools used in this study were unable to truly capture the potential benefits from DBS, this study presents a feasible framework for carrying out clinical trials of neuromodulation in pediatric patients with extreme physical disabilities and communication difficulties. Most pediatric DBS studies rely upon either retrospective analyses or summary of case reports, and our study provides additional evidence of the feasibility of testing clinical trial designs, as well as of collecting data in this exceptionally challenging group of patients. Given the large response variability between patients, novel N-of-1 experimental designs with multiple cross-over double-blinded replications of effective and ineffective stimulation per participant, rather than classic parallel group comparisons, may be better suited to determine DBS efficacy in acquired dystonia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord 2013;28:863–873. [PubMed: 23649720]
2. Mink JW. Special concerns in defining, studying, and treating dystonia in children. Mov Disord 2013;28:921–925. [PubMed: 23893449]
3. Koman LA, Smith BP, Shilt JS. Cerebral palsy. The Lancet 2004;363:1619–1631.

4. Kupsch A, Benecke R, Müller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. N Engl J Med 2006;355:1978–1990. [PubMed: 17093249]
5. Bruggemann N, Kuhn A, Schneider SA, et al. Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. Neurology 2015;84:895–903. [PubMed: 25653290]
6. Koy A, Hellmich M, Pauls KA, et al. Effects of deep brain stimulation in dyskinetic cerebral palsy: a meta-analysis. Mov Disord 2013;28:647–654. [PubMed: 23408442]
7. Burchiel KJ. Thalamotomy for movement disorders. Neurosurg Clin N Am 1995;6:55–71. [PubMed: 7696875]
8. Cardoso F, Jankovic J, Grossman RG, Hamilton WJ. Outcome after stereotactic thalamotomy for dystonia and hemiballismus. Neurosurgery 1995;36:501–507; discussion 507–508. [PubMed: 7753350]
9. Broggi G, Angelini L, Giorgi C. Neurological and psychological side effects after stereotactic thalamotomy in patients with cerebral palsy. Neurosurgery 1980;7:127–134. [PubMed: 6999375]
10. Patel A, Deeb W, Okun MS. Deep Brain Stimulation Management of Essential Tremor with Dystonic Features. Tremor Other Hyperkinet Mov (N Y) 2018;8:557–557. [PubMed: 29971197]
11. Sanger TD, Liker M, Arguelles E, et al. Pediatric Deep Brain Stimulation Using Awake Recording and Stimulation for Target Selection in an Inpatient Neuromodulation Monitoring Unit. Brain Sci 2018;8.
12. Wolf ME, Blahak C, Saryyeva A, Schrader C, Krauss JK. Deep brain stimulation for dystonia-choreoathetosis in cerebral palsy: Pallidal versus thalamic stimulation. Parkinsonism Relat Disord 2019;63:209–212. [PubMed: 30718219]
13. Jinnah HA, Neychev V, Hess EJ. The Anatomical Basis for Dystonia: The Motor Network Model. Tremor Other Hyperkinet Mov (N Y) 2017;7:506–506. [PubMed: 29123945]
14. Marshall RD, Collins A, Escolar ML, et al. A Scale to Assess Activities of Daily Living in Pantothenate Kinase-Associated Neurodegeneration. Mov Disord Clin Pract 2019;6:139–149. [PubMed: 30838313]
15. Kaufman AS, Kaufman NL. Kaufman Brief Intelligence Test, Second ed. Blookington, MN 2004.
16. Kamphaus RW, Reynolds CR. Behavior Assessment System for Children-Third Edition (BASC-3): Behavioral and Emotional Screening System (BEES). Bloomington, MN 2015.
17. Association AP. American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, 5th edition ed. Arlington, VA 2013.
18. Starr PA, Markun LC, Larson PS, Volz MM, Martin AJ, Ostrem JL. Interventional MRI-guided deep brain stimulation in pediatric dystonia: first experience with the ClearPoint system. J Neurosurg Pediatr 2014;14:400–408. [PubMed: 25084088]
19. Olaya JE, Christian E, Ferman D, et al. Deep brain stimulation in children and young adults with secondary dystonia: the Children's Hospital Los Angeles experience. Neurosurg Focus 2013;35:E7.
20. Kupsch A, Tagliati M, Vidailhet M, et al. Early postoperative management of DBS in dystonia: Programming, response to stimulation, adverse events, medication changes, evaluations, and troubleshooting. Movement Disorders 2011;26:S37–S53. [PubMed: 21692111]
21. 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. The Lancet Neurology 2009;8:709–717. [PubMed: 19576854]
22. Krauss JK, Loher TJ, Weigel R, Capelle HH, Weber S, Burgunder J-M. Chronic stimulation of the globus pallidus internus for treatment of non-DYT1 generalized dystonia and choreoathetosis: 2-year follow up. 2003;98:785.
23. Marks WA, Honeycutt J, Acosta F Jr., et al. Dystonia due to cerebral palsy responds to deep brain stimulation of the globus pallidus internus. Mov Disord 2011;26:1748–1751. [PubMed: 21491490]
24. 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;55:567–574. [PubMed: 23452222]
25. Treves T, Korczyn AD. Progressive Dystonia and Paraparesis in Cerebral Palsy. European Neurology 1986;25:148–153. [PubMed: 3948889]

26. Tustin K, Elze MC, Lumsden DE, Gimeno H, Kaminska M, Lin J-P. Gross motor function outcomes following deep brain stimulation for childhood-onset dystonia: A descriptive report. Eur J Paediatr Neurol 2019;23:473–483. [PubMed: 30846371]
27. Koy A, Weinsheimer M, Pauls KAM, et al. German registry of paediatric deep brain stimulation in patients with childhood-onset dystonia (GEPESTIM). Eur J Paediatr Neurol 2017;21:136–146. [PubMed: 27424797]
28. Prudente CN, Hess EJ, Jinnah HA. Dystonia as a network disorder: what is the role of the cerebellum? Neuroscience 2014;260:23–35. [PubMed: 24333801]
29. Sanger TD. A Computational Model of Deep-Brain Stimulation for Acquired Dystonia in Children. Front Comput Neurosci 2018;12:77–77. [PubMed: 30294268]
30. Hedera P, Phibbs FT, Dolhun R, et al. Surgical targets for dystonic tremor: Considerations between the globus pallidus and ventral intermediate thalamic nucleus. Parkinsonism & Related Disorders 2013;19:684–686. [PubMed: 23611688]
31. Fasano A, Bove F, Lang AE. The treatment of dystonic tremor: a systematic review. J Neurol Neurosurg Psychiatry 2014;85:759–769. [PubMed: 24167042]
32. Qin Y, Li Y, Sun B, et al. Functional Connectivity Alterations in Children with Spastic and Dyskinetic Cerebral Palsy. Neural Plast 2018;2018:7058953. [PubMed: 30186320]
33. Brown EG, Bledsoe IO, Luthra NS, Miocinovic S, Starr PA, Ostrem JL. Cerebellar Deep Brain Stimulation for Acquired Hemidystonia. Mov Disord Clin Pract 2020;7:188–193. [PubMed: 32071938]
34. Nakano N, Miyauchi M, Nakanishi K, Saigoh K, Mitsui Y, Kato A. Successful Combination of Pallidal and Thalamic Stimulation for Intractable Involuntary Movements in Patients with Neuroacanthocytosis. World Neurosurgery 2015;84:1177.e1171–1177.e1177.
35. Burbaud P, Rougier A, Ferrer X, et al. Improvement of severe trunk spasms by bilateral high-frequency stimulation of the motor thalamus in a patient with chorea-acanthocytosis. Movement Disorders 2002;17:204–207. [PubMed: 11835468]
36. Ghika J, Villemure JG, Miklossy J, et al. Postanoxic generalized dystonia improved by bilateral Voa thalamic deep brain stimulation. Neurology 2002;58:311–313. [PubMed: 11805266]
37. Kim AR, Chang JW, Chang WS, Park ES, Cho SR. Two-year outcomes of deep brain stimulation in adults with cerebral palsy. Ann Rehabil Med 2014;38:209–217. [PubMed: 24855615]
38. 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 Psychiatry 2014;85:1239–1244. [PubMed: 24591458]
39. Elze MC, Gimeno H, Tustin K, et al. Burke-Fahn-Marsden dystonia severity, Gross Motor, Manual Ability, and Communication Function Classification scales in childhood hyperkinetic movement disorders including cerebral palsy: a ‘Rosetta Stone’ study. Dev Med Child Neurol 2016;58:145–153. [PubMed: 26616635]
40. 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;16:501–508. [PubMed: 22258088]

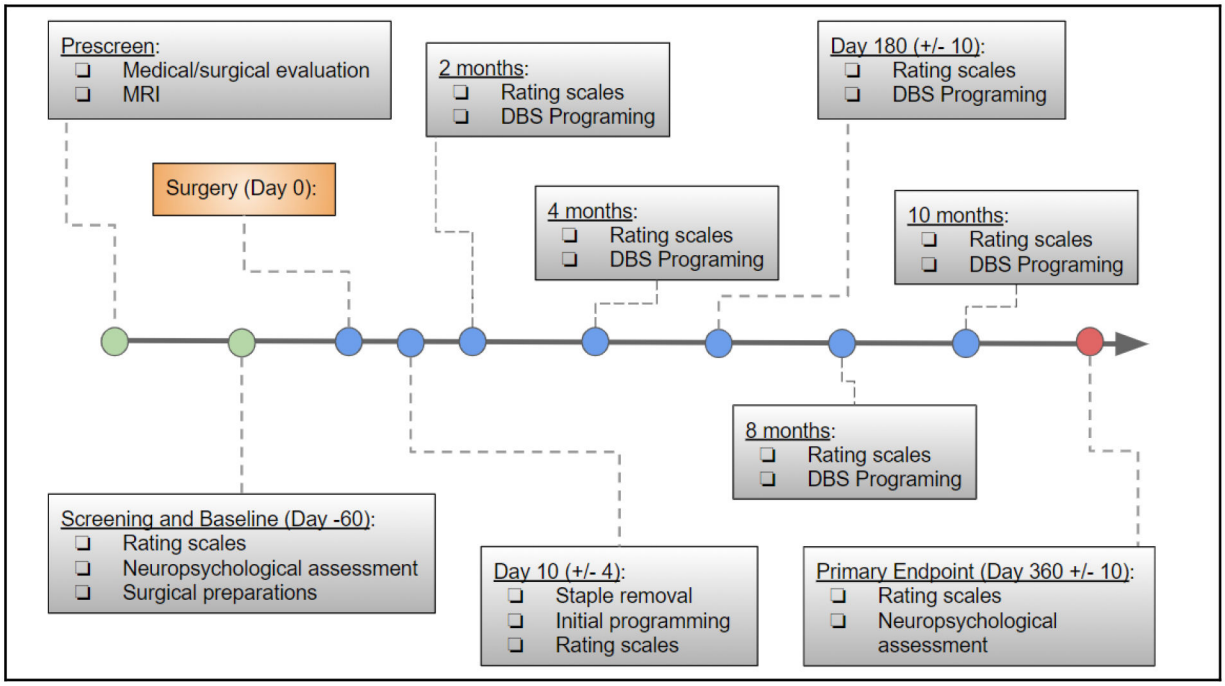

Figure 1.
Participant Flow Chart

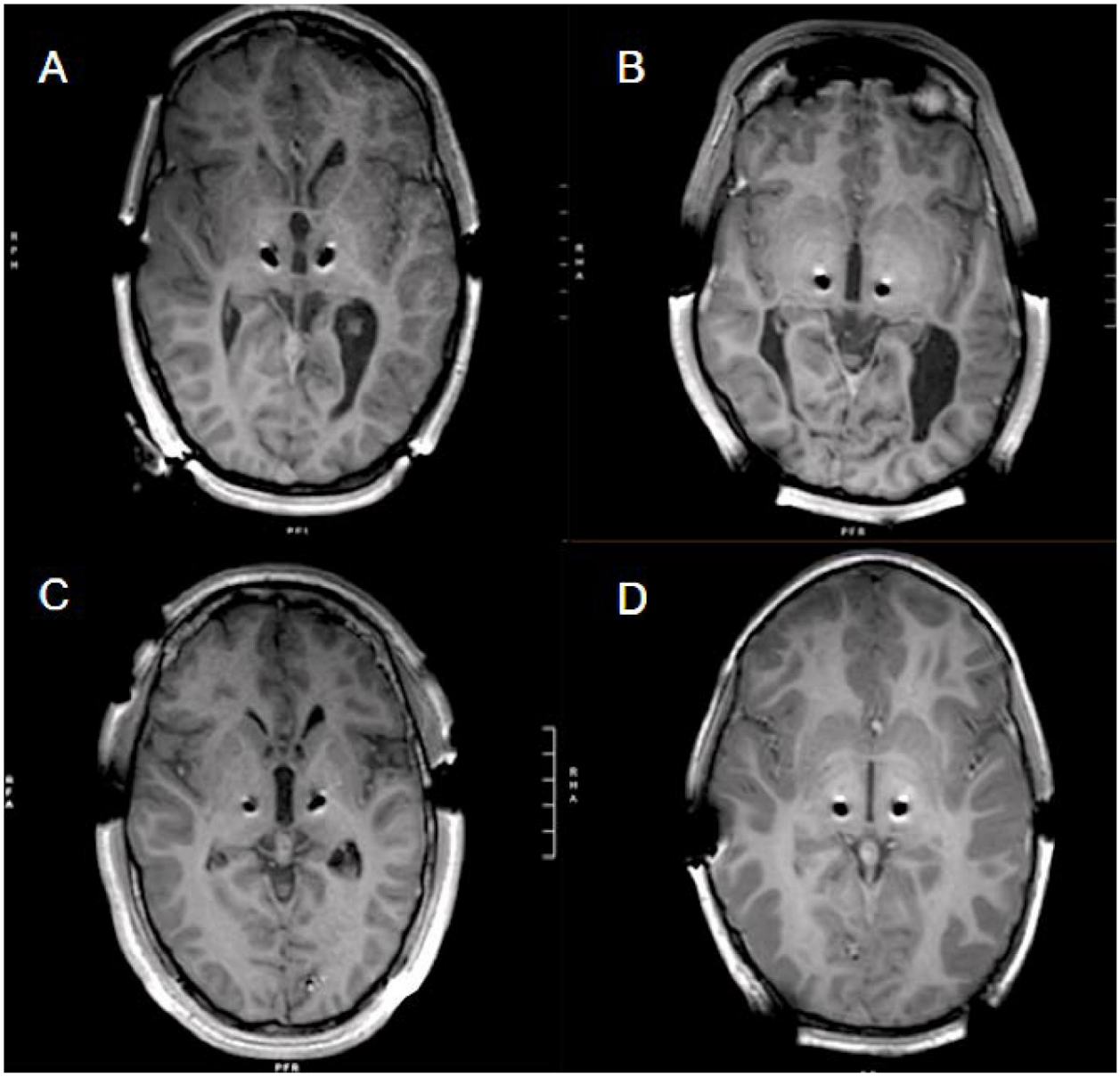

Figure 2.
DBS lead tip location.
Axial 3T T1 MRI images showing DBS lead tip artifact for each participant (A. Participant 1, B. Participant 2, C. Participant 3, and D. Participant 4.

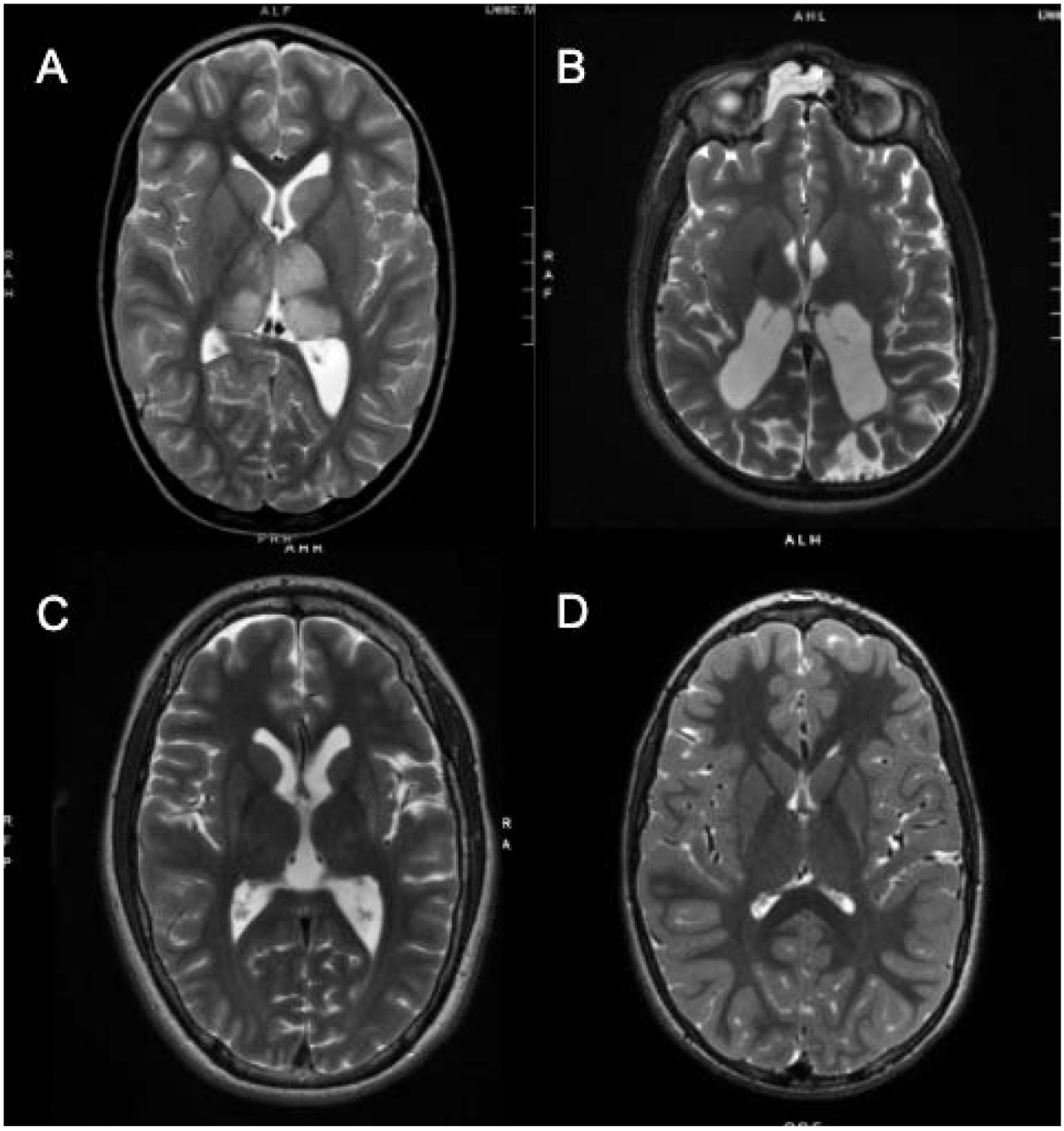

Figure 3.

Axial T2 preoperative MRI images from all participants

A) Participant 1: preoperative MRI showed vermis and pontine atrophy, abnormal cerebellar signal and diffusely diminished supratentorial white matter with thinning of corpus callosum. B) Participant 2: His preoperative imaging at age 19 showed posterior predominant cerebral as well as bilateral thalamic volume loss and posterior corpus callosum atrophy. C) Participant 3: Brain MRI prior to surgery showed global cerebral, bilateral thalamic and left more than right putaminal volume loss, as well as Wallerian degeneration of bilateral internal capsules and cerebral peduncles. D) Participant 4: MRI brain showed

very mild T2 hyperintensities in bilateral pallidum, posterior putamen, ventrolateral thalami and perirolandic regions, representing sequelae of prior injury.

Table 1:

DBS Electrode Coordinates and Settings

Participant	Side	AC-PC Distance	Tip Lateral Coordinate	Tip anteroposterior coordinate	Tip vertical coordinate	Approach angle sagittal	Approach angle coronal	Final DBS settings (12 months)
1	L	24.92	9.08	8.09	5.22	32.64	14.42	C+1−2−, 1.5V, 60μsec, 90Hz
	R		8.11	8.09	5.22	31.64	13.89	0−1−2+, 1.0V, 60μsec, 90Hz
2	L	27.56	10.23	4.2	5.3	22.48	8.52	C+1−, 3.5V, 90μsec, 140Hz
	R		10.7	2.71	4.55	32.74	6.29	C+1−, 3.5V, 90μsec, 140Hz
3	L	23.44	10.25	6.03	3.58	40.82	16.04	C+1−, 2.9V, 60μsec,140Hz
	R		12.92	5.03	2.33	12.46	9.61	C+2−, 2.8 V, 60μsec,140Hz
4	L	24.44	10.29	7.1	3.41	16.53	8.86	C+1−, 3.5V, 60μsec, 140Hz
	R		10.14	7.1	3.41	18.84	8.26	C+1−, 3.3V, 60μsec, 140Hz

*Patient 3 DBS settings from 17 month follow-up

**Tip anteroposterior and vertical coordinates measured from the posterior commissure

Table 2.

Demographic and clinical characteristics

ID	Sex	Age	Race/Ethnicity	Duration of Symptoms (years)	Diagnosis	GMFCS*	Medications and Procedures
1	F	14	White/Not Hispanic	8	West Nile encephalitis at age 7	IV	• Procedures: Left hip intertrochanteric osteotomy with open reduction, posterior spine arthrodesis T2 to pelvis • Pre-DBS medications: baclofen, diazepam, dantrolene, carbidopa/levodopa, botulinum toxin injections • Post-DBS medications: diazepam as needed, botulinum toxin injections • Previously failed medications: trihexyphenidyl
2	M	19	White/Hispanic	19	Dystonic cerebral palsy, premature birth at 26 weeks	IV	• Procedures: bilateral hamstring tendon lengthening, dental restoration • Pre-DBS medications: baclofen • Post-DBS medications: baclofen • Previously failed medications: trihexyphenidyl, carbidopa/levodopa
3	M	16	Other/Not Hispanic	16	Dystonic cerebral palsy, neonatal encephalopathy	V	• Procedures: selective dorsal rhizotomy, bilateral hip osteotomies, strabismus repair, testicular detorsion • Pre-DBS medications: baclofen, botulinum toxin injections • Post-DBS medications: diazepam • Previously failed medications: none
4	F	9	White/Not Hispanic	9	Dystonic cerebral palsy, neonatal encephalopathy	II	• Procedures: none • Pre-DBS medications: none • Post-DBS medications: none • Previously failed medications: carbidopa/levodopa

*Gross Motor Function Classification System for Cerebral Palsy

Table 3.

Primary outcomes for efficacy

	BFMDRS (unblinded)					BFMDRS (blinded)				
Participant	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**
1	77.5	60	78	**0.5**	**0.6**	60.5	80	62.5	**2**	**3.3**
2	92	77	69	**-23**	**-25**	66	69.5	70	**4**	**6.1**
3	79	55.5	67.5	**-11.5**	**-14.6**	63	75.5	80.5	**17.5**	**27.8**
4	53	-	28	**-25**	**-47.2**	40	-	33	**-7**	**-17.5**
	BADS (unblinded)					**BADS (blinded)**				
Participant	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**
1	21	20	23	**2**	**9.5**	24	23	22	**-2**	**-8.3**
2	25	23	22	**-3**	**-12**	21	23	25	**4**	**19**
3	22	19	25	**3**	**13.6**	21	27	26	**5**	**23.8**
4	17	-	14	**-3**	**-17.6**	13	-	17	**4**	**30.8**

* 12 month blinded outcomes unavailable for participant 3. Results from 10 month evaluation used for above calculations.

Table 4.

Modified Ashworth Scale Spasticity Ratings

Upper Extremity Averages				
Participant	**Baseline**	**6 months**	**12 months**	**% change**
1	1.57	0.63	2.83	**80.3**
2	2.25	2.5	2	**-12.5**
3	3	1.33	3.13	**4.3**
4	0.75	-	0.75	**0**
Lower Extremity Averages				
Participant	**Baseline**	**6 months**	**12 months**	**% change**
1	1.38	0.63	2.67	**93.5**
2	2.13	2	1.5	**-29.6**
3	2.5	0.88	2.5	**0**
4	0.63	-	1	**58.7**

Table 5.

Quality of Life Outcomes

BFMDRS Disability Total					
Participant	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**
1	28	26	24	**-4**	**-14.3**
2	25	24	24	**-1**	**-4**
3	22	21	24	**2**	**9.1**
4	13	-	6	**-7**	**-53.8**
Modified UPDRS II Total					
Participant	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**
1	38	36	-	-	-
2	35	33	-	-	-
3	34	29	26	**-8**	**-23.5**
4	20	-	17	**-3**	**-15**
PedsQL™ Total					
Participant	**BL**	**6 mo.**	**12 mo.**	**Δ**	**% change**
1	49	48	44	**-5**	**-10.2**
2	32	41	32	**0**	**0**
3	42	37	19	**-23**	**-54.8**
4	44	-	25	**-19**	**-43.2**

*BL = baseline assessment

**Note that both the BFMDRS Disability and Modified UPDRS II scales are scored such that higher numbers indicated greater disease severity and lower numbers indicate lesser disease severity. Similarly, the PedsQL™ scale is scored such that higher numbers indicate decreased health-related quality of life and lower numbers indicate higher health-related quality of life.