Deep brain stimulation in a pediatric dystonia patient with cochlear implants and mitochondrial disorder: novel application of a frameless stereotactic system and navigating the anesthesia choice and neurosurgical complexities. Illustrative case

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BACKGROUND This report presents a case of medically refractory dystonia in a pediatric patient successfully treated with bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) while under general anesthesia by using microelectrode recordings (MERs) with intraoperative computed tomography (CT).

OBSERVATIONS The patient was an 18-year-old female with primary dystonia secondary to mitochondrial Leigh syndrome. Her past medical history was significant for complex partial epilepsy and hearing loss treated with cochlear implants. Her cochlear implants precluded anatomical targeting via magnetic resonance imaging. Additionally, the patient could not tolerate awake surgery with MER. The decision was made to proceed with bilateral STN DBS with intraoperative CT with the patient under general anesthesia. The patient’s cochlear implants made standard frame placement difficult, so navigation was performed with the Nexframe system. Recordings were obtained with the patient under general anesthesia with ketamine, dexmedetomidine, and remifentanil. At the 3- and 6-month follow-ups, the patient demonstrated marked improvement in dystonia without neurological complications.

LESSONS This is the first case of dystonia secondary to Leigh syndrome treated with DBS. Additionally, the authors describe the novel use of the Nexframe for DBS lead placement in a pediatric patient. This demonstrates that STN DBS with the use of MER and intraoperative CT can be a safe and effective method of treating dystonia in certain pediatric patients.

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KEYWORDS dystonia; deep brain stimulation; Nexframe; microelectrode recordings; anesthesia; pediatric

Deep brain stimulation (DBS) involves stereotactically implanted electrodes imparting high-frequency electrical stimulation with proven efficacy in various movement disorders.1–3 Its application in dystonic patients dates back several decades.4–8 As DBS has progressed, the globus pallidus internus (GPI) and subthalamic nucleus (STN) have been identified as optimal targets for treating dystonia.9–11 Stereotactic implantation has also evolved from coordinate-based systems for targeting to a neurophysiology-guided procedure with microelectrode recordings (MERs) in awake patients to anatomical targeting with high-resolution magnetic resonance imaging (MRI) in asleep patients.12,13

Pediatric dystonia is often refractory to medications and has been increasingly treated with DBS. The most common target is the GPI followed by the STN. Both have shown good results, with long-term improvement in motor outcomes lasting more than 5 years after DBS electrode placement.14

ABBREVIATIONS BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; CT = computed tomography; DBS = deep brain stimulation; GPI = globus pallidus internus; MCP = midcommissural point; MER = microelectrode recording; MRI = magnetic resonance imaging; PW = pulse width; STN = subthalamic nucleus; TIVA = total intravenous anesthesia.

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DBS poses a challenge in some populations, thus necessitating the accommodation of patients who are unable to tolerate awake surgery. For example, many pediatric patients are less likely to tolerate awake surgery as a consequence of both their young age and possible neurocognitive deficits related to their underlying disease. In this study, we report the novel use of a frameless navigation system for bilateral STN DBS in a pediatric patient in whom cochlear implants precluded MRI. Because awake surgery was not permissible, targeting relied on computed tomography (CT) scanning and MERs. We describe the novel use of the Nexframe system (Medtronic) for DBS lead placement in a pediatric patient with refractory dystonia secondary to Leigh syndrome. Dystonia severity was evaluated using the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) at baseline and at follow-up visits at 3 and 8 months.

Illustrative Case

A 19-year-old female had a history of Leigh syndrome secondary to mitochondrial disorder, bilateral hearing loss treated with cochlear implants, dystonia, and epilepsy. She had a long history of developmental delay as well as regression. Her cochlear implants precluded the use of MRI. On preoperative brain CT, she had symmetric hypodensities of the putamen and caudate head consistent with mitochondrial encephalopathy. Prior genetic testing demonstrated 3 separate mutations in the GFM2 gene (1 considered pathologic with 2 variants of unknown significance).

On exam, she had significant dystonic posturing, particularly in her left upper extremity and paraspinal muscles, with significant gait issues that had failed to respond to oral medications, bracing, and femoral osteotomies. She also had localization-related symptomatic epilepsy and epileptic syndromes with complex partial seizures. Multiple medications had failed; thus, she was evaluated in our multidisciplinary movement disorder clinic. After extensive discussion regarding intrathecal baclofen pump placement versus DBS, her family opted for DBS.

Identifying the STN Using Microelectrode Data

Targets were selected on standard atlas-based coordinates based off the midcommissural point (MCP) with confirmation via Schaltenbrand-Wahren atlas overlay. Final coordinates of the right and left STN were 12 mm lateral, 3 mm posterior, and 4 mm inferior to the MCP (Fig. 1). These targets were then refined with MERs. During surgery, successful STN targeting was performed with Nexframe navigation and MERs (Fig. 2). Recordings were obtained with the patient under general anesthesia with ketamine, dexmedetomidine, and remifentanil for a total length of 6 mm on the left side and 7 mm on the right side.

Figures 3 and 4 consist of postoperative CT scans demonstrating DBS lead placement with the intended targeting planning overlay. Asymmetry in lead placement resulted from deeper lead placement on the left side. The Nexframe is typically screwed into the outer table, and the MERs equipment is mounted onto this. Given the weight of the recording equipment, after placement of the right-sided lead, we noted that the weight of the recording equipment was slightly deflecting the trajectory anteriorly. However, given the robust MER signals and after discussion with a neurophysiologist, it was decided intraoperatively to leave the leads as placed. After removal of the Nexframe, we noted that the anterior screw was slightly loose and 1–2 threads too superficial. Final measured errors for the right lead were 0.8 mm on the probe’s eye view with a 5.7-mm depth error (deep). Final measured errors for the left lead were 8.5 mm on the probe’s eye view with a ~3.3-mm depth error (shallow).

DBS Programming

The stimulation parameters for the left and right STN at the time that DBS was turned on were as follows. For the right STN, stimulation of contacts 8, 9, and 10 caused left leg tightening at an amplitude of 1.5 V, pulse width (PW) of 60 msec, and frequency of 85 Hz. Stimulation of contact 11 caused no symptoms up to an amplitude of 3 V, PW of 60 msec, and frequency of 85 Hz. The following contacts were kept active (amplitude, PW, frequency, respectively): 10a, at 1.3 V, 60 msec, 85 Hz; 10b, at 0.2 V, 60 msec, 85 Hz; 10c, at 0.5 V, 60 msec, 85 Hz. Contacts 9a (1.1 V, 60 msec, 85 Hz) and 9b (0.3 V, 60 msec, 85 Hz) were also kept active. For the left STN, stimulation of contacts 0 and 1 caused right leg tightening at an amplitude of 1.5 V, PW of 60 msec, and frequency of 85 Hz. Stimulation of contacts 2 and 3 caused no symptoms up to an amplitude of 3 V, PW of 60 msec, and frequency of 85 Hz. Contact 2 was kept active at an amplitude of 2.5 V, PW of 60 msec, and frequency of 85 Hz. Since the time of initially turning on the DBS, the patient has continued parameter adjustments with incremental benefit.

Follow-Up

Given her response clinically, no lead revision has been necessary in this patient. Table 1 demonstrates BFMDRS scores pre-DBS and at the 3- and 8-month follow-ups. At the 2-week follow-up, the
The patient had some issues with headache and lethargy, prompting a return to the hospital, but CT was negative. We found that she had stopped taking baclofen, and when it was restarted, her symptoms resolved. Her tremors had also resolved.

At the 3-month follow-up, there was significant improvement in her gait, and she was continued on baclofen 20 mg 3 times daily. There was improvement in her right foot drawing in. Additionally, her gait was improved, with less torsional dystonia of the spine, and she demonstrated more dexterity of the left hand. However, her right hand continued to be the most affected and limited independence in activities of daily living. She had slightly improved speech with no change in dysarthria. Last, she was quite underweight prior to DBS, and she had gained almost 20 pounds at the time of this visit.

At the 8-month follow-up, the patient reported fewer falls, less torsion of the trunk with better posture, and less flexion posturing of the left upper extremity. Her caregiver stated that they had noticed marked benefit from DBS, with approximately 80% overall improvement. The patient was able to use her hand (improving with therapy) to perform some functions such as opening doors and holding objects, which she had been unable to do previously. She was also walking much better, with much improved posture. She had no eye or mouth spasms, and there was only moderate difficulty understanding her speech.

**Patient Informed Consent**

The necessary patient informed consent was obtained in this study.

**Discussion**

**Observations**

To the best of our knowledge, this is the first report of using the Nexframe system for DBS lead placement in a pediatric patient. It demonstrates that STN DBS with the use of MERs and intraoperative CT can be a safe and effective method for treating dystonia in certain pediatric patients.

**Decision to Treat**

One study found that some of the most important factors that pediatric movement disorder specialists consider when referring patients for DBS are age, symptom severity, etiology, genetic status, and the clinician’s perceived risks and benefits of DBS for the pediatric population.
Some authors have identified great symptomatic improvement in patients with primary dystonia DYT1. However, no specific guidelines on when to treat pediatric dystonia with DBS exist, including the impact of DYT1 results and primary versus secondary causes. Our patient with primary dystonia secondary to Leigh disease was DYT1−, yet has shown significant alleviation of her symptoms, suggesting that patients with this pathology may be reasonable DBS candidates. Future studies clarifying the optimal target and stereotactic technique (e.g., awake vs asleep, with or without MERs vs anatomical targeting) are needed.

Frame-Based Versus Frameless Stereotaxy

There are a variety of DBS lead delivery mechanisms including traditional frame-based stereotaxy, frameless options, the Nexframe stereotactic system using StealthStation navigation (Medtronic Inc, Dublin, Ireland), and the FHC STARFix System (FHC Inc, Bowdoin, ME, USA). Frame-based techniques have a fixed frame that completely surrounds the patient’s head. These remain the gold standard in terms of accuracy and include the Leskell frame or Cosman-Roberts-Wells frame. Frameless options utilize skull-mounted aiming systems that are registered to a patient’s head in order to plan a trajectory using fiducials or intraoperative imaging, as well as a navigation system that then aligns the surgical trajectory with the plan. Studies have shown that an error of less than 2–3 mm is permissible to allow accurate lead placement and an improved clinical outcome.

One meta-analysis of frame-based and frameless systems for DBS found that, while likely not clinically significant, there was a significant increase in target error when comparing frameless with frame-based techniques. The increased accuracy of frame-based techniques was 0.3037 mm, 0.0305 mm, 0.1630 mm, and 0.0285 mm for x, y, z, and vector coordinates, respectively, as compared with frameless techniques. Regardless, frameless techniques still fall within the 2- to 3-mm error window, as demonstrated by various studies. While we could not use a frame-based technique in this patient because of her cochlear implants, the frameless technique did provide some benefits, including a shorter operating time and increased patient comfort.

The main consideration for Nexframe tower placement in pediatric patients is skull thickness. A skull thickness of at least 4 mm at the location of the Nexframe tower placement is recommended to ensure adequate purchase. The Nexframe, especially with the recording equipment, can be quite bulky and inflict a significant torque force. In our case, deflection of the right lead occurred after navigation was used to perfect the trajectory. In order to avoid this, one should ensure that all of the screws are flush and that there is no toggle of the Nexframe after placement of the recording equipment. Otherwise, the Nexframe presents a great option for children to obviate the need for conventional pin fixation.

Targeting the STN in Pediatric Dystonia

In a recent systematic review, 91% of pediatric patients with dystonia underwent GPi DBS system implantation. The optimal stimulation target, specifically with regard to mitochondrial disorders, has yet to be elucidated. Typical targeting techniques are awake with MERs or asleep without MERs but with anatomical targeting. In our patient, her young age and high anxiety prevented us from performing awake surgery. Additionally, anatomical targeting was not possible given her cochlear implants and the inability to perform MRI. Therefore, we resorted to asleep CT-guided targeting with MERs.

![Postoperative axial, sagittal, coronal, and probe’s eye view computed tomography (CT) scans demonstrating right DBS lead placement with planning overlay. Blue lines demonstrate the planning trajectory, and the red dots demonstrate the intended target. The yellow lines are the planned trajectory for the right-sided lead, while the blue lines are the left-sided plans. Final measured errors were 0.8 mm on the probe’s eye view with a 5.7-mm depth error (deep).](image)
In our patient, the decision was made to target the STN because she had a known history of symmetric hypodensities in the bilateral putamen and basal ganglia on CT. These lesions were likely caused by her Leigh disease, a mitochondrial encephalopathy that can affect the basal ganglia, periaqueductal gray and cerebral peduncles. Additionally, changes in the putamina seem to be a consistent feature. While the GPi is the most commonly targeted site for treatment of pediatric dystonia, our patient’s history of Leigh disease and signs of damage to her basal ganglia made the GPi a less than ideal target.

An important consideration in this case, especially with the lack of anatomical detail given the inability to perform MRI, was the target structure size. The typical mean volume of the GPi ranges from 400 to 500 mm³, whereas the STN typically ranges from 150 to 300 mm³.\(^{27,28}\) Another consideration, especially as regards indirect targeting via coordinates based on the anterior commissure–posterior commissure system, is consistency of location. The GPi demonstrates significant variability in size, shape, and position relative to the MCP; thus, indirect targeting of this structure has largely been abandoned.\(^{29-31}\) Recent studies have also clarified that the highest beta power is more represented in the areas within the STN where DBS will be most effective, as shown by analyzing the local field potential distribution in patients implanted with segmented leads for directional stimulation.\(^{32}\)

Anesthesia Choice
Another important consideration in choosing to target the GPi in this patient was the neurophysiological data, as MER in asleep patients can be affected by anesthesia choice. The anesthesia choice must be carefully reviewed prior to its induction to avoid neuronal suppression that would nullify recording potential. The STN recording can disappear or be distorted if a patient is over-anesthetized. It has been noted that propofol is the most common sedative for asleep DBS with MER. However, the downside of this is propofol’s action on GABA receptors, activating the GABAA receptor and potentiating its response to GABA.\(^{33-36}\) The GPi contains GABAergic cells and thus is particularly prone to inadequate MER in asleep cases, while the STN consists of glutamatergic neurons.\(^{33-36}\) Several authors have noted that, although propofol may attenuate STN signals, identification of the structure’s borders remains possible.\(^{36-38}\) Precedex has also shown minimal effect on GPi and STN recordings; it functions as a specific and selective \(\alpha_2\)-adrenoceptor agonist with

**TABLE 1. Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) scores at baseline and follow-up**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Preoperative</th>
<th>3-Mo FU</th>
<th>8-Mo FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>General speech/swallow</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Eyes</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mouth</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Speech/swallow</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Neck</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arm</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Trunk</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Leg</td>
<td>3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

FU = follow-up.
no impact on GABA-receptors. The STN, on the other hand, receives adrenergic input, yet similarly, has not seen MER affected by dexmedetomidine.

Typically, total intravenous anesthesia (TIVA) is administered during DBS and neuromonitoring cases since the volatile agents can affect monitoring. The most commonly used drugs are propofol and remifentanil. However, propofol strongly inhibits complex I as well as other sites of oxidative phosphorylation and the utilization of fatty acids, so it is not an ideal choice for drug for someone with a mitochondrial disease. Volatile anesthetics also suppress oxidative phosphorylation but are minimally metabolized, so the choice to do a TIVA over volatiles is likely attributable to the type of surgery and institutional preferences. For our patient, TIVA was run using ketamine, dexmedetomidine, and remifentanil, as those drugs have been reported to be well tolerated. Rocuronium was used a few times throughout the case when motor stimulation was not needed.

Literature Outcomes for Pediatric Dystonia

One review examined outcomes of pediatric dystonia cases treated with DBS with a follow-up of 5 or more years. They found that long-term motor outcomes showed improvement in BFMDRS ranging from 2.5% to 93.2%, depending on dystonia subtype. The pediatric patients with idiopathic, inherited, or isolated dystonias fared better than those with acquired dystonias. Higher quality-of-life scores were also reported post-DBS, although these data continue to be limited.

The vast majority of pediatric dystonia cases have been treated with stimulation of the GPi. With specific regard to stimulation of the STN, one 10-year follow-up of pediatric patients undergoing STN DBS found that the average improvement in the BFMDRS motor score was over 75% at the 1-year follow-up and 90% at the 10-year follow-up. Likewise, there was an improvement in BFMDRS disability score of 70% and 87% at the 1- and 10-year follow-ups, respectively. Notably, improvements seen at the 10-year follow-up were significantly better than those at the 1-year follow-up.

Lessons

This case illustrates asleep frame-based implantation of bilateral DBS electrodes in the STN for medically refractory dystonia in a pediatric patient. The technique of using the Nextraframe system and interpretation of MERs for side-effect testing under a selective anesthesia plan is discussed. Preoperative and postoperative BFMDRS scores demonstrated functional improvement at follow-up.

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References


Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Desai, Grossen, Stocco, Sahgal, Conner. Acquisition of data: Desai, Grossen, Schenk, Ramsey, Sahgal, Conner. Analysis and interpretation of data: Desai, Grossen, Ramsey, Sahgal, Conner. Drafting of the article: Grossen, Shi, Conner. Critically revising the article: Desai, Shi, Stocco, Conner. Reviewed submitted version of the manuscript: Desai, Grossen, Shi, Stocco, Ramsey, Conner. Approved the final version of the manuscript on behalf of all authors: Desai. Administrative/technical/material support: Grossen, Shi, Conner. Study supervision: Conner.

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