Current and future indications for deep brain stimulation in pediatric populations

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Deep brain stimulation (DBS) has proven to be an effective and safe treatment option in patients with various advanced and treatment-refractory conditions. Thus far, most of the experience with DBS has been in the movement disorder literature, and more specifically in the adult population, where its use in conditions such as Parkinson disease has revolutionized management strategies. The pediatric population, however, can also be afflicted by functionally incapacitating neurological conditions that remain refractory despite the clinicians’ best efforts. In such cases, DBS offers an additional treatment alternative. In this paper, the authors review their institution’s experience with DBS in the pediatric population, and provide an overview of the literature on DBS in children. The authors conclude that DBS in children can and should be considered a valid and effective treatment option, albeit in highly specific and carefully selected cases. (DOI: 10.3171/2010.5.FOCUS1095)

KEY WORDS • deep brain stimulation • dystonia • spasticity • epilepsy • children

Over the past few decades, the introduction of DBS has revolutionized the management of several functional disorders affecting the adult population. Deep brain stimulation currently plays an established role in the management of movement disorders, providing durable symptom relief and improved quality of life with minimal morbidity and side effects. In addition, the role of DBS procedures is currently under investigation in many other neurological and psychiatric disorders previously considered to be beyond the realm of neurosurgery. In spite of such exciting progress, the application of this therapeutic paradigm to functional disorders affecting the pediatric population remains limited. This review summarizes our institutional experience with DBS in children and discusses the current and potential future role of DBS procedures in the multidisciplinary management of pediatric functional disorders.

Institutional Experience

From 2001 to the present, we have treated 6 children (2 boys, 4 girls) with DBS procedures (Table 1). The mean age at the time of treatment for this cohort was 13 years (range 8–18 years). Clinical indications for DBS treatment included 3 patients with DYT1 dystonia, 1 with secondary dystonia (viral encephalitis), 1 with glutaric acidemia Type 1, and 1 patient who presented with dystonia of unknown origin. All patients had undergone unsuccessful medical management of their movement disorders prior to consultation. Prior functional procedures included bilateral pallidotomy in 1 patient. A second patient had undergone previous pallidotomy and insertion of bilateral GPi electrodes and presented with worsening dystonia and hardware failure. The 4 remaining patients had not undergone previous surgical procedures. Surgery in this series included bilateral GPi DBS insertion in 4 patients and bilateral subthalamic zona inserta DBS insertion in 1 patient. One patient underwent revision of their GPi DBS electrodes and pulse generator. There were no procedural or postoperative complications observed in this series. Following DBS insertion, patients were followed up in the neurosurgery clinic as well as at the movement disorders clinic at Toronto Western Hospital. The mean follow-up duration for available patients was 32 months (range 1–77 months), which was limited by the fact that 5 of 6 patients included in this study were referred from institutions outside Canada and did not frequently return to Canada. Follow-up was unavailable in 1 patient. No DBS-related side effects were documented in this series under normal stimulation parameters. Clinical outcomes

Abbreviations used in this paper: CP = cerebral palsy; DBS = deep brain stimulation; GPi = globus pallidus internus; OCD = obsessive-compulsive disorder.
TABLE 1: Summary of pediatric patients undergoing DBS at our institution

<table>
<thead>
<tr>
<th>Age (yrs), Sex</th>
<th>Indication/Previous Treatment</th>
<th>DBS target</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>8, F</td>
<td>primary dystonia of unknown origin</td>
<td>bilat GPi</td>
<td>no improvement</td>
</tr>
<tr>
<td>12, F</td>
<td>secondary dystonia</td>
<td>subthalamic zona inserta</td>
<td>no follow-up available</td>
</tr>
<tr>
<td>18, M</td>
<td>DTY1 dystonia w/ previous pallidotomy &amp; GPi DBS</td>
<td>bilat GPi (revised GPi electrodes &amp; pulse generator)</td>
<td>improvement of motor symptoms, ambulation</td>
</tr>
<tr>
<td>15, M</td>
<td>DYT1 dystonia w/ previous pallidotomy</td>
<td>bilat GPi</td>
<td>improvement of motor symptoms, ambulation</td>
</tr>
<tr>
<td>9, F</td>
<td>DYT1 dystonia</td>
<td>bilat GPi</td>
<td>improvement of motor symptoms, ambulation</td>
</tr>
<tr>
<td>16, F</td>
<td>dystonia, glutaric acidemia Type 1</td>
<td>bilat GPi</td>
<td>mild improvement in motor symptoms</td>
</tr>
</tbody>
</table>

were available for 5 patients. All patients with DTY1 dystonia who were treated with bilateral GPi DBS showed significant improvement in their motor symptoms; 2 patients who were confined to a wheelchair due to axial and limb dystonia gained the ability to walk independently after surgery. One patient with progressive dystonia due to glutaric acidemia Type 1 who was treated using bilateral GPi DBS showed mild improvement of her right upper and lower extremities 2 months postoperatively. Finally, 1 patient with progressive dystonia affecting all extremities of an unknown origin was treated with bilateral GPi DBS and showed no significant improvement in her symptoms (Table 1).

Current Indications for Pediatric DBS

Currently, most DBS procedures in the pediatric population have been performed for movement disorders, specifically dystonia. Because most centers combine their pediatric and adult patients when reporting results, it is difficult to estimate the number of pediatric patients who have undergone implantation with DBS electrodes. Furthermore, there are currently no prospective studies examining DBS for pediatric movement disorders. Nevertheless, several centers have reported their experiences with DBS in children, some with promising results, indicating a possible therapeutic benefit for DBS in this population.

Dystonia remains the most frequent current indication for surgical intervention in children. Dystonia is a disorder of dysfunctional neuronal-muscle firing, leading to involuntary and sustained muscle contractions, causing abnormal twisting and posturing. Primary dystonia is due to inborn mutations in the DYT gene, of which there are several kinds, and in which DYT1 is the most common. Secondary dystonia is acquired, and most frequently is related to CP or neonatal asphyxia, or is the result of brain degeneration or accumulation of organic deposits such as iron or bilirubin. Due to the multiple different causes of secondary dystonia, this population is subsequently more diverse and heterogenous, making broad generalizations of treatment efficacy more difficult. Nevertheless, DBS has been applied in children suffering from both primary and secondary dystonia (Table 2). There is a long history of the use of thalamotomy and pallidotomy in children with dystonia; more recently, pallidotomy was reintroduced with striking results. This development led to the rapid introduction of pallidal DBS for dystonia, first in adults and then quickly in children. Among the earliest reports of DBS for dystonia in a child came from Coubes et al. in 1999, in which an 8-year-old child underwent GPi DBS for primary dystonia, with significant functional outcomes at 3 years. One study reported the use of GPi DBS in 4 children with primary generalized dystonia following the failure of medical therapy, and found that dystonic movements were significantly improved at 6 months postoperatively. Importantly, targets for adult and pediatric patients with dystonia remain the same, as most centers have used the GPi as the target. A further study involving GPi DBS that examined 10 patients, of which 3 were children, also found significant improvements in both dystonic movements and functional disability after 2 years. One of the largest case series to date specifically included pediatric patients involved 12 patients with childhood onset dystonia, of which 8 had primary and 4 secondary dystonia. In this study, all but 1 patient derived a significant functional benefit from GPi DBS. Such results are similar to a more recently reported series in which 15 pediatric patients underwent bilateral pallidal DBS. This series reported a minimum improvement in dystonic posturing of 40% in all patients at 1 year, with substantial improvements in disability scores for all children.

The rarity of secondary dystonia in children, and the heterogeneity of the patient population, has resulted in a scarcity of reported outcomes of DBS for these diverse conditions. Cases of children undergoing DBS for Cockayne syndrome and Lesch-Nyhan syndrome have been reported, all with positive results. Despite these seemingly positive outcomes, it appears that children with secondary dystonia respond less robustly to treatment in general, and to DBS in particular. Clearly, the rarity of these disorders precludes the design of adequate trials, but it appears that the experiences of multiple institutions supports continued research into the application of DBS for secondary dystonia in medically refractory cases.

Tremor is uncommon in the pediatric literature, and when present, is typically secondary to neurodegenerative disorders or otherwise secondary causes. The experience with DBS in tremor in adults, using the ventral intermediate nucleus of the thalamus as the target, has been
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TABLE 2: Summary of DBS studies for primary dystonia in children*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Indication</th>
<th>No. of Patients</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coubes et al., 1999</td>
<td>primary dystonia (dystonia musculorum)</td>
<td>1</td>
<td>dramatic improvement in symptoms at 6 wks</td>
</tr>
<tr>
<td>Zorzi et al., 2005</td>
<td>primary &amp; secondary dystonia</td>
<td>12 (8 primary, 4 secondary)</td>
<td>dystonic movements significantly decreased in 11 patients</td>
</tr>
<tr>
<td>Alterman et al., 2007</td>
<td>primary dystonia</td>
<td>15</td>
<td>7 discontinued medications, 6 reduced medications by &gt; 50%</td>
</tr>
<tr>
<td>Parr et al., 2007</td>
<td>idiopathic generalized dystonia</td>
<td>4</td>
<td>significant reductions in dystonic movements in all patients</td>
</tr>
<tr>
<td>Magariños-Ascone et al., 2008</td>
<td>primary dystonia</td>
<td>10 (3 children)</td>
<td>significant reductions in dystonic movements in all children w/ DBS</td>
</tr>
</tbody>
</table>

* The DBS target for all studies was the GPI.

reviewed elsewhere, and its application has been explored for essential tremor and tremor associated with multiple sclerosis. In children, a single case report exists of the successful treatment of a Holmes tremor secondary to a thalamic abscess with DBS of the ventral intermediate nucleus of the thalamus.38

Tic disorders, such as Tourette syndrome, are among the most common neurological disorders of childhood. In addition to causing significant functional and social impairment, they often coexist with other, primarily psychiatric, disorders such as OCD and/or attention deficit disorder. The management of tics is primarily pharmacological, with surgical alternatives, particularly in children, reserved for only the most refractory and challenging cases. The target and timing for DBS, the optimal surgical strategy, and patient selection are all controversial topics, generating significant research.45 The largest reported series to date of DBS for Tourette syndrome comes from Italy,43 in which 18 patients underwent surgery, of whom 4 were under the age of 20 at the time of operation. Patients all had tic onset during adolescence or younger and the surgical target was the centromedian thalamic nucleus. All 4 pediatric patients experienced significant reductions in tic severity.

Surgery for Tourette syndrome and other tic disorders is complicated by the unpredictable natural history of tics in general. Tics in a substantial number of pediatric patients spontaneously remit by the age of 20, leading many authors to question the role of invasive neuromodulation in children.38 We agree with this assessment, and believe that surgical management of Tourette syndrome in the pediatric population should be reserved for only the most refractory and challenging cases. Apart from the devastating burden of uncontrolled tics, they often coexist with other, primarily psychiatric, disorders such as OCD and/or attention deficit disorder. As a result, some researchers have sought the areas with most promise and controversy will be in the overlapping literature on Tourette Syndrome. The domain of DBS for psychiatric indications, specifically with a focus on the impulse control disorders, such as OCD and anorexia nervosa.

Obssessive-Compulsive Disorder

Currently, DBS OCD programs have focused on the adult population, with some pediatric patients included only in the overlapping literature on Tourette Syndrome. The OCD experience with DBS has been thoroughly reviewed elsewhere.16,42 Importantly, the use of DBS for refractory OCD has been subjected to a double-blind randomized study, whose positive result indicates that the technology is indeed an effective form of last-resort treatment.35 Such studies satisfy important criteria for the application of this technology to pediatric populations, where the threshold for surgical intervention is typically higher.

Disorders of impulse control likely share common neuroanatomical and physiological roots. Accordingly, similar structures may underlie their pathophysiology, and their disruption may lead to improvements in overt pathological behavior. As a result, some researchers have sought to implant DBS electrodes in patients with comorbid conditions, and, either retrospectively or prospectively, observe the effects on both conditions. For example, I paper reports improvement in an intractable eating disorder with subgenual cingulate stimulation for depression.25 The use of DBS for the treatment for eating disorders is still in the early investigational stages, but as most eating disorders, anorexia nervosa in particular, strike in adolescence, the use of surgery for debilitating and life-threatening disease in some pediatric patients remains a future possibility.

Epilepsy

Epilepsy is one of the most common neurological conditions affecting children, with approximately 20,000 to 45,000 cases diagnosed in the US annually.39,20 While approximately two-thirds of children will attain seizure remission with antiepileptic medication, a significant proportion will go on to develop a chronic seizure disorder. Apart from the devastating burden of uncontrolled seizures and antiepileptic side effects, children with epi-
lepsy are also at increased risk for other comorbidities including developmental delay, depression, anxiety disorders, substance abuse, suicide, and sudden death.39,44,46 The effects of childhood epilepsy on marital status, education, employment, and overall quality of life are also significant.44 Until recently, the role of neurosurgery in pediatric epilepsy has been limited mostly to patients with structural abnormalities of the brain. In the setting of cortical dysplasia, vascular malformations, neoplasms, and mesial temporal sclerosis, resection of epileptogenic foci leads to alleviation of seizures in as many as 60–87% of cases.5,8,18,23,54 For children with generalized, nonlocalizable refractory seizures, an additional smaller proportion may derive benefit from palliative neuromodulatory procedures such as vagus nerve stimulation of disconnective procedures such as corpus callosotomy or functional hemispherectomy.6,17,20 Of the 30% to 40% of children whose seizures fail to be controlled despite multiple antiepileptic medications, a significant number will not be eligible for surgery due to multifocal, nonlocalizable disease or the identification of an epileptic focus arising from eloquent brain tissue.9

Deep brain stimulation has recently emerged as an effective alternative treatment modality for adults with medically refractory epilepsy. Although the anatomical substrates and circuits responsible for seizure initiation and propagation are largely unknown, the results of preclinical animal studies have lead to the identification of several promising anatomical targets that have recently been explored in prospective human clinical trials. Among the most common targets investigated in adult DBS studies are the hippocampus, subthalamic nucleus, and thalamus.14,19 Among these studies, Velasco et al.38 demonstrated that hippocampal stimulation reduced interictal spikes as well as the frequency of complex partial and tonic-clonic seizures in patients with medically refractory temporal lobe epilepsy. Benabd et al.4 treated a child with inoperable cortical dysplasia and refractory epilepsy with subthalamic nucleus DBS and observed an 83% improvement in seizure frequency as well as improvement of motor function. A number of studies have investigated the effect of anterior nucleus of the thalamus stimulation on medically refractory seizures, including I at our institution.3,22,28,32 Bilateral anterior nucleus of the thalamus DBS was associated with a reduction in seizure frequency in all 6 patients in our study, an effect that was independent of stimulator parameters.5 Although we found little short-term improvement in patients who underwent centromedian nucleus of the thalamus stimulation for medically refractory epilepsy, results from other groups demonstrated promising results, particularly in patients with absence and generalized seizures in the setting of Lennox-Gastaut syndrome.5,49 The long-awaited preliminary results from a large, multiinstitutional, prospective randomized double-blinded trial of anterior nucleus of the thalamus stimulation in 110 adults with medically refractory epilepsy (SANTE trial) have recently been made available. Patients treated with anterior nucleus of the thalamus DBS experienced a statistically significant reduction in seizure frequency compared with sham-treated participants, an effect that increased over time.36

In addition to conventional DBS systems, epilepsy patients will also soon benefit from advances made in the field of brain-machine interfaces. This paradigm involves the collection and processing of neural activity to help drive external devices.50 In this model, implanted depth or surface electrodes can be used to detect epileptiform activity that is sent to an implantable processing unit, which subsequently delivers an electrical response to the brain, thereby abolishing seizure activity. The use of implantable closed-loop systems have shown promising results in small clinical studies5 and have recently been investigated in a prospective clinical trial. In a randomized, double-blind, sham-controlled study of the implantable Responsive Neurostimulation System (Neuropace Inc.) in adults with medically refractory partial-onset seizures, 47% of patients experienced a 50% or greater reduction in seizure frequency.40

Given all these data, the future of DBS for medically refractory epilepsy is encouraging and will hopefully provide important alternative treatment options for children with debilitating seizure disorders. The ideal targets and stimulator parameters for individual seizure disorders will be better appreciated as larger collaborative studies are completed. Given the significant long-term effects of chronic childhood epilepsy on educational attainment, employment, marital status, and psychological health into adulthood, we may see the application of DBS techniques earlier in the disease process in an effort to reduce these long-term impairments. As children are increasingly incorporated into prospective trials of novel treatment paradigms, DBS will undoubtedly emerge as an important tool in the neurosurgeon’s armamentarium against pediatric epilepsy.

Spasticity

Spasticity has been defined as a “motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (or tone) resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome.”30 In the pediatric population, the vast majority of spasticity is observed in the setting of CP, which occurs in approximately 3 or 4 per 1000 children.51 Stroke, head injury, and spinal cord injury make up important alternative causes of spasticity in children. Functional disability in CP may be due to spasticity alone but may also be associated with other movement disorders such as tremor, dystonia, or choreoathetosis. The distinction between spasticity, CP, and secondary movement disorders can be challenging in the pediatric population, potentially requiring different treatment approaches. Although spasticity may arise from a number of causes, the pathophysiological mechanisms are often characterized by an increase in afferent excitatory input or increased sensitivity) to spinal motor neurons combined with a reduction in inhibitory impulses to the same effectors. As such, current pharmacological and surgical interventions are aimed at restoring the balance between these opposing conditions.

Management of spasticity requires a multidisciplinary approach, careful patient selection, and a realistic appreciation of the objectives and limitations of each individual
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therapeutic intervention. The mainstay of spasticity management for over 15 years has been medical management with baclofen, diazepam, and other agents that are used to treat diffuse, generalized spasticity. Botulinum toxin has been successfully employed to provide temporary relief of focal spasticity. Modern neurosurgical interventions currently offered to children with spasticity include selective dorsal/posterior rhizotomy and implantation of intrathecal baclofen pumps. Whereas dorsal rhizotomy and intrathecal baclofen improve functional disability related to spasticity in children with CP, a significant proportion of children will exhibit symptoms related to comorbid movement disorders. Although dorsal rhizotomy has no effect on dystonia, chorea, or athetosis, a significant proportion of children with dystonia will derive benefit from intrathecal baclofen, albeit at much higher doses than those used to treat spasticity.1

Although spasticity accounts for a significant proportion of movement disorders affecting children, the application of DBS strategies to this population has been limited. Promising results have been found in GPi stimulation for secondary dystonias and choreoathetosis, but few studies have included children. Among adult studies, Vidailhet et al. treated 13 adults with dystonia-choreoathetosis CP with GPi DBS and observed significant improvements in functional movement scores, functional disability, pain, and mental health–related quality of life. In one of the first pediatric DBS reports, Thompson et al. treated 2 patients with choreiform movement disorders using thalamic DBS, one of whom had CP. In that 15-year-old patient with bilateral choreiform movements of the upper extremities, unilateral DBS of the ventral intermediate nucleus of the thalamus lead to pronounced improvement in the contralateral chorea as well as improved ease of handwriting and eating. Both the patient’s and parents’ satisfaction lead to consideration of another DBS procedure to treat the other extremity. In addition to its role as a primary treatment modality, the effect of combined DBS and conventional surgical interventions for mixed movement disorder CP subtypes also remains undefined. In one study, Woon et al. treated 3 children with dystonia secondary to CP and suggested that DBS may be used to treat the primary functional disease while associated spasticity may be synergistically controlled by intrathecal baclofen infusion. Overall, these studies highlight the significant heterogeneity in movement impairments among children with CP. An understanding of the cortical, subcortical, and spinal reorganization that occurs following early CNS insults will be paramount to elucidating potential DBS targets for children with spasticity.

Ethical Issues in Pediatric DBS

The threshold for surgical intervention in a child, no matter the indication, always needs to be higher than that in the adult. Children are not small adults, and their ongoing brain development, both structural and physiological, can have an influence on the mechanism of DBS, particularly given the plasticity of the developing brain and its circuits. As an example, a recent expert panel has suggested that DBS not be used in children for psychiatric indications, as the long-term effects of chronic brain stimulation are unknown. Deep brain stimulation is, however, a potentially powerful tool that may significantly alter a child’s quality of life, and we propose that strict ethical guidelines and criteria be employed prior to any DBS application in the pediatric age-group.

Strict attention needs to be given to the informed consent process, and to a comprehensive discussion of the risks, benefits, and treatment expectations and goals. Parents need to be made aware of the largely investigational use of DBS for refractory conditions, be they psychiatric or motor, and that the use of DBS necessitates continuous battery changes and the potential for hardware complications. Furthermore, the treating surgeon needs to be aware of all possible treatment options, medical and surgical, for their patients, to gauge whether their patient has truly reached a treatment refractory stage. The burden of acquiring sufficient evidence rests with the treating team, to prove that DBS can provide an effective and safe last resort for treatment.

Conclusions

Pediatric patients will certainly benefit from the continued development of DBS technology for the management of refractory neurological, and with time, psychiatric conditions. Currently, several studies support the use of DBS for movement disorders in highly selected patients, with ongoing research exploring additional, exciting indications. The future of pediatric functional neurosurgery will focus on the development of safer, smaller, and more flexible technology that will improve the child’s quality of life, while minimizing exposure to surgical risk.

Disclosure

Dr. Lozano serves as a consultant to Medtronic and St. Jude Medical.

Author contributions to the study and manuscript preparation include the following. Conception and design: all authors. Drafting the article: Lipsman, Ellis. Critically revising the article: all authors. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Lozano.

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