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REHABILITATION TECHNOLOGY (R HARVEY, SECTION EDITOR)

Neuromodulation in Childhood Onset Dystonia: Evolving Role of Deep Brain Stimulation

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Abstract

Purpose of Review This review will provide an update on the current status of deep brain stimulation in pediatric onset dystonias.
Recent Findings Dystonia is a complex movement disorder that may occur in isolation or in combination with other abnormalities of tone and posture. The dystonias represent a heterogeneous group of movement disorders that can be progressive, painful, and severely disabling. Genetic and extrinsic factors may influence the treatment response. Pharmacologic treatment often has limited effectiveness and unacceptable, unwanted effects. Neuromodulation by deep brain stimulation (DBS) is a targeted therapy that continues to evolve as a treatment option for children with medically refractory dystonia due to a variety of etiologies. We share some insights from our surgical experience with 124 children with dystonia treated by DBS and review the current literature on the use of DBS in pediatric onset dystonia.
Summary Advances in surgical options make the surgery more tolerable for young children. Secondary dystonia, in particular cerebral palsy, is more common than primary genetic etiologies. Both may respond to DBS, which may be considered once medical management has failed. Data sharing through registry platforms such as PEDiDBS is a vital component for expanding our knowledge base.

Keywords Dystonia · Genetic dystonia · Spasticity · Pediatric · Status dystonicus · Cerebral palsy

Introduction

Movement involves the sequential firing of a series of neuronal circuits involving interconnected brain regions that are then delivered through the spinal cord to the muscles. Movement disorders are the result of abnormal or dysfunctional firing patterns that arise from disturbances at the cortical or subcortical levels.

Hypertonia can be subdivided into spasticity, dystonia, and rigidity. Spasticity is defined as velocity-dependent resistance to passive stretching of the muscle. Dystonic movements are "typically patterned, twisting, and may be tremulous." [1•, 2].

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While spasticity is generally considered a disorder of the corticospinal pathways, dystonia is derived from the subcortical basal ganglia extrapyramidal system. Dystonia can be tonic, phasic, or paroxysmal.

Disorders involving abnormal movement in children are often complex. Dystonia can be the sole feature, but more often is seen in conjunction with other abnormalities of tone or movement, making medical management particularly complex. This is seen in both genetic and acquired causes of dystonia. The overall approach to the treatment of movement disorders has been reviewed [3•]. There is little class 1 or 2 evidence for any current medical or surgical interventions for dystonia. Dopaminergic precursors or direct agonists may be effective in many forms of dystonia. In addition to cumulative clinical experience, there is also evidence that trihexyphenidyl can be an effective oral option [4••]. Concerns have been raised about the potential cognitive implications of this drug in children, and more recently about the long latency effects of prolonged anti-cholinergic exposure on the aging brain [5]. This is further complicated by the range of medications with anti-cholinergic properties (antiseizure,

antihistamine, Parkinson's) used to treat comorbidities that often exist in people with dystonia. There is no data on the long-term effects of early and prolonged use on the developing brain.

Neuromodulation is "the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body." [6]. Therapies may include targeted electrical or magnetic stimulation, or infusion of medications into the cerebrospinal fluid using intrathecal medication delivery. Targeted neuromodulation by deep brain stimulation (DBS) involves the delivery of electrical current to modulate neuronal impulses.

In the USA, DBS was approved for the treatment of essential Parkinson's disease in the late 1990s with no age restriction. DBS was approved for use in dystonia beginning at age 7 years in the USA with a Humanitarian Device Exemption (HDE) in 2003 [7]. European regulators did not include the same age restriction that the US FDA applied.

Our institutional experience includes one hundred thirty-one patients implanted since September 2007, including 124 initial implants for dystonia.

Targets and Mechanisms of Action

While there is an ongoing debate regarding the actual mechanisms behind DBS, general concepts include the following: (1) masking of extraneous electrochemical "noise," (2) direct stimulation of neurons or axons resulting in downstream effects, (3) long-term creation of alternative pathways via neuronal plasticity. A newer proposal is that "DBS dissociates input and output signals, resulting in the disruption of abnormal information flow through the stimulation site". [8]. There is support for all of these hypotheses, and it seems likely that there are multiple overlapping mechanisms at play. Certainly, with tremor, the effects of DBS can be seen immediately. While it is generally acknowledged that the overall effects in dystonia may take months or longer to be appreciated, our experience has been that in most cases, some changes can be seen even with initial programming. In addition, some patients with dystonia can have the system turned off for variable periods of time, from hours to months, without return of symptoms, whereas in others, cessation of therapy can result in near-immediate status dystonicus. We have seen the entire range in our population, and it does not appear specific to the underlying pathology.

As with any technology or medication, clinical experience and the art and science of medicine have advanced our understanding and application of available therapies. Children younger than seven years of age have safely undergone DBS for status dystonicus or severe refractory dystonia, albeit with some concern that leads might have to be re-implanted at a later date due to interval growth of the head and neck [9].

The globus pallidus (GPi) was the approved target for dystonia based on a limited population of patients with primary genetic dystonia. We have generally preferred GPi as the target for dystonia and hyperkinesis arising from both genetic and acquired etiologies. Recent experience from other centers supports this approach [10]. Our evolving understanding of the complexity of extrapyramidal connectivity between the basal ganglia and cerebellum is leading to consideration of alternative targets and an expanded range of symptoms that may respond to DBS**.** Just as GPi can be an alternative target for Parkinson's tremor, the subthalamic nucleus (STN) can be an alternative target site for dystonias not responsive to modulation of the GPi [11]**.** We have successfully utilized the STN in two siblings with pyruvate decarboxylase deficiency, where significant destruction of the GPi was apparent by an MRI scan.

Adapting the concept of mapping by depth electrode from epilepsy colleagues, Sanger has introduced the use of stereo-EEG microelectrode recording and macro-stimulation to clarify the electrophysiology of basal ganglia connectivity to aid in alternative target selection in patients with secondary dystonias [12•]. We have begun applying the macro-stimulation in a limited set of patients. As this involves additional surgical procedures, it is reserved for special circumstances such as failed stimulation of the primary target, severely abnormal anatomy on imaging, or complex mixed movement disorders. This provides an opportunity to individualize treatment in patients with aberrant connectivity.

As currently applied, DBS is generally considered a treatment for tremor and dystonia. Sporadic reports have suggested that cerebellar stimulation may reduce spasticity but this has yet to be fully validated [13].

Surgical Considerations in Children

DBS for tremor and Parkinson's was developed using intraoperative microelectrode recordings and clinical testing since the effects on tremor can be immediate. With the HDE approval for dystonia, similar techniques were applied to the GPi with varying degrees of somatotopic mapping to aid in presumed ideal lead placement. The effects on dystonia are often not as immediately apparent, thus diminishing some of the clinical value of intraoperative testing. Anesthesia significantly modifies dystonia in many cases. This technique of twilight anesthesia surgery can be even more problematic in a pediatric population, especially in the context of severe hyperkinesis that accompanies some forms of dystonia. Intraoperative safety was a concern in young patients and those with marked hyperkinesis, especially involving the head and neck area.

We began our pediatric DBS program in 2007 and performed our first eighty-four DBS cases for dystonia using microelectrode recording (MER) and twilight anesthesia. Overtime, we evolved to a protocol relying primarily on dexmedetomidine for anxiolysis and modest sedation along with the aggressive use of scalp blocks [14, 15]. Experience has shown that this is an effective agent at reducing dystonic and associated dysautonomia as well. We additionally utilized child life extensively in the OR to provide distraction techniques and as an additional monitor of stress and anxiety. MER surgery requires the presence of additional operating room personnel moving about the operating room, thus increasing the infection risk and the added time commitment of support personnel for monitoring and testing. The electrical signals in dystonia can be more difficult to discern than the typical tremor cell firing pattern with potential negative effects on the reliability of MER for localization. Robotic-assisted MER guidance may improve the accuracy of MER-guided surgery. Image-guided frame-based lead placement procedures demonstrate an accuracy range of 0.6 to 2 mm on average. This improved to < 1.1 mm using ROSA-guided MER-adjusted system [16].

The introduction of image-guided technology resulted in improved accuracy of lead placement [17] and has supplanted the use of MER in our institution. Since 2015, all of our DBS leads ($n = 47$ patients; 97 leads) are placed under general anesthesia using intraoperative image guidance. Only a single lead which dislodged during placement of the stim-lock has had to be revised utilizing this surgical approach and accuracy has improved to submillimeter accuracy.

Surgery can be done as a single-stage or as a separate procedure for lead placement with follow-up surgery for IPG implant. We initially believed that the single-stage procedure would be less stressful and more efficient for patients; however, we were concerned about an unacceptable rate of surgical infections. This prompted a change to the dual-stage procedure, each with an overnight hospitalization. With this modification, we saw a decreased infection rate from 7 in 67 (10%) to 1 in 60 (1.6%). We have used only perioperative antibiotics and do not generally administer postoperative antibiotics.

Clinical Experience: Selected Disorders

Since our first surgery in September 2007, one hundred thirty-one patients have undergone DBS lead placements, including 127 patients initially implanted in our center. All but three were done for dystonia. Two patients with essential tremor and one with DRPLA-related ataxia were also implanted. Figure 1 shows the breakdown by diagnostic category. Secondary dystonias ($n = 89$) most commonly cerebral palsy–related dystonia ($n = 36$) are substantially more common reasons for implant than primary dystonias. Of the thirty-five primary dystonia syndromes, Dyt-1 ($n = 12$) is the most commonly identified genetic dystonia.

As DBS for dystonia has a humanitarian device exemption, all patients are consented under a rigorous research-based protocol and entered into an IRB approved database. Of 131 lead implant surgeries (127 initial implants, 4 revisions performed on patients from elsewhere), our first 83 (September 2007 through May 2011) were done using conscious sedation and microelectrode guidance. Since June 2011, all patients are done as a two-stage procedure under general anesthesia using the clearpoint intraoperative MRI-guided system. One hundred twenty-four of the 127 patients had dystonia.

GPi is our preferred target, although STN has been used in siblings with pyruvate dehydrogenase deficiency who had a loss of the globus pallidus following metabolic crisis. One patient with post-traumatic-acquired unilateral myoclonus dystonia had an implant of contralateral GPI and VIM thalamus.

Spasticity

Deep brain stimulation of the basal ganglia does not appear to affect spasticity directly. No large-scale or long-term human studies have confirmed the efficacy of this approach and there is no current clinically approved treatment using cerebellar stimulation. Treatment of refractory spasticity is currently managed pharmacologically (intrathecal baclofen) or by ablative surgical procedures to interrupt pathways (rhizotomy, neurectomy).

Primary Progressive Dystonias with Presumed or Known Genetics

There is extensive experience with primary presumed genetic dystonia in childhood. Benefits are sustained for more than a decade [18].

Dyt-1 limb onset isolated torsion dystonia is caused by autosomal dominant mutations in the TOR1A gene. Due to the variable penetrance of gene expression, clinical manifestations range from asymptomatic to severe dystonia. Often poorly responsive to medications, DYT-1 has been the gold standard for DBS treatment of dystonia. Our own experience with 15 pediatric Dyt-1 patients has paralleled this overall response to GPi DBS. STN stimulation may offer relief to GPI-unresponsive patients [19•].

A closely related disorder is caused by mutations in the THAP gene (Dyt-6). Limited experience suggests that DYT-6 THAP–related dystonia seems to be more variably responsive to DBS therapy [20, 21]. In a recent review, only 6 small series of patients were identified, with follow-up ranging from 2 months to several years and response rates best described as moderate [22].

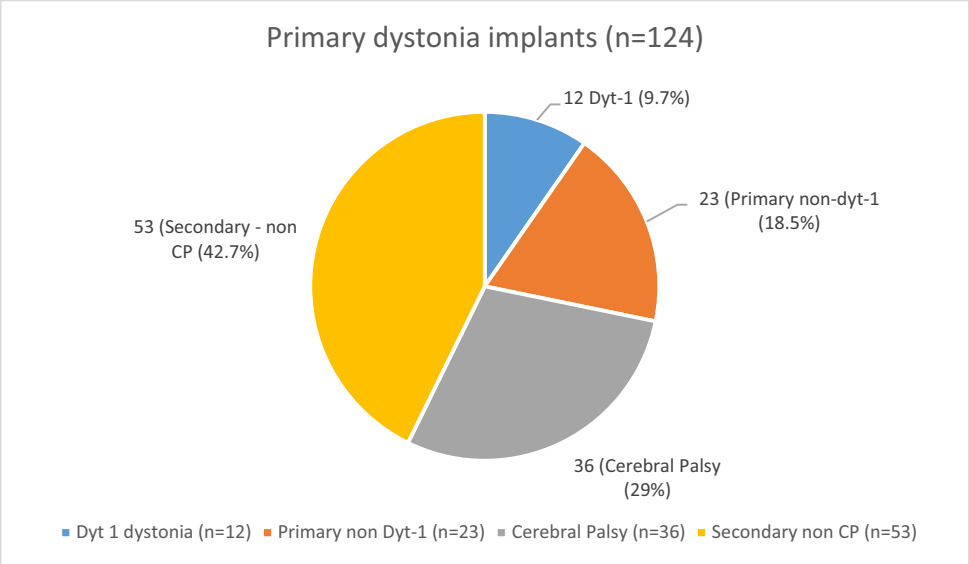

Fig. 1 Initial DBS implants for dystonia from 2007 to present ($n = 124$)

Myoclonus Dystonia Syndrome (Dyt-11)

Myoclonus dystonia is a clinical syndrome consisting of a complex of movement disorders including dystonia, myoclonus, and tremor, often associated with progressive psychiatric comorbidities (anxiety, depression). About 60–70% of Dyt-11 is due to an autosomal dominantly inherited mutation in the epsilon-sarcoglycan gene (SGCE). This disorder may be more common in children than initially appreciated [23]. Medications including trihexyphenidyl and zonisamide may be effective. Zonisamide in particular has been effective in reducing both myoclonus and dystonia in this population and should be tried before considering DBS [24•].

There are now numerous reports and series of myoclonus dystonia syndrome being responsive to DBS with GPI or ventral intermediate nucleus (VIM) [25, 26]. A few patients with comorbid Dyt-1 and Dyt-11 have also been reported as responsive to GPI DBS after failing to respond to VIM stimulation [27]. We prefer GPi in our children ($n = 4$) with primary genetic myoclonus dystonia with ($n = 3$) or without ($n = 1$) a confirmed mutation in the SGCE and all have responded well. One patient with post-traumatic unilateral myoclonus dystonia secondary to a remote traumatic brain with structural injury responded well to dual stimulation of the contralateral GPi and VIM thalamus with a near-complete resolution of symptoms.

Dystonia Related to Other Genetic Disorders

Responsiveness to DBS has been seen in several other genetic disorders with intact basal ganglia anatomy. A full review is beyond the scope of this paper. One disorder of particular interest is GNAO-1. GNAO-1 is a complex disorder due to mutations located on 16q13 with variable phenotypic expression ranging from mild dyskinesias to severe dystonia, cognitive impairment, and refractory epilepsy with associated encephalopathy [28]. Recurrent bouts of status dystonicus and status epilepticus may occur in severely affected patients. There are numerous reports of dramatic GPi-DBS responsiveness in this population, often done at a very young age due to refractory status dystonicus [29, 30].

Of our three GNAO-1-positive patients, the one with the most severe phenotype was implanted to abort medically refractory status dystonicus and responded dramatically with no recurrent episodes in more than 6 months. We have also seen improvement in hyperkinesis in other genetic disorders with a similar mixed motor phenotype including Pitt-Hopkins syndrome. Reduction of disabling hyperkinetic movements in dystonic disorders has also been reported [31].

Cerebral Palsy and Other Acquired Dystonias

Cerebral palsy represents a unique challenge. By definition, cerebral palsy is a syndrome due to multiple etiologies with the common finding of a motor disorder with or without comorbidities. CP is the most common cause of motor disability in children, affecting as many as 2.9/1000 children**.** Motor abnormalities involve both tone (spasticity, hypotonia) and movement (dystonia, choreoathetosis, rigidity). With the exception of the mildest forms of spastic diplegia, dystonia is a near-universal finding in cerebral palsy. The dystonia, therefore, cannot be managed in isolation. Measuring outcomes is also complicated by the fact that our current dystonia rating scales were not designed for mixed motor disorders. All involved in managing children with cerebral palsy recognize

that even small gains can have major life-changing impacts beyond what can be measured. Often the improvement, while not reflected by current rating scales, is reported subjectively by patients or caretakers.

Although the robustness of DBS responsiveness may not be as consistent as in primary genetic disorders, DBS has demonstrated beneficial effects on many in patients with cerebral palsy [32•].

We have previously reported that some patients with mixed cerebral palsy respond to DBS in a parallel fashion with those with Dyt-1 dystonia [33]. Younger patients with mixed cerebral palsy respond better than older patients with fixed skeletal deformities [34]. Although the response in patients with cerebral palsy may be less consistent and robust than in primary dystonias, sustained improvement in motor and cognitive performance has been reported [35, 36]. The need for more age-dependent development outcome measures has been highlighted [37•].

The evidence for DBS is on par with the level of support for most pharmacologic interventions including intrathecal baclofen [4••].

Process/Measurement Scales/Perceived Outcomes: Where Do We Go from Here?

It is important to have an experienced team in order to effectively guide children and their families through the complex decision-making process involved in making the commitment to undergo DBS. Our process involves serial team assessments with incremental education. Information is tailored to the family's level of comfort. Whenever possible, the child is involved in the ongoing decision-making process, aided by a child life professional. Consistent with clinical research guidelines that are in place for HDE-approved devices, our informed consent process approved by our institutional review board involves verbal or written assent from the patient when appropriate [14]. This process is vital, given the vulnerability of the patient population due to young age, degree of physical suffering, and often concomitant cognitive impairment of the patient [38].

Families identified the opportunity for their children to maximize their potential as the key desire that made perceived risks of brain surgery worthwhile [39]. During our presurgical evaluation and family education process, several of our older teen patients with dyskinetic cerebral palsy expressed optimism and a fear of looking back later and regretting that they did not take advantage of this opportunity, even if they did not ultimately benefit from the procedure. Postoperatively, outcomes were variable and one required re-operation; but almost none expressed regrets about having undergone the procedure.

Outcome Measures

Many pediatric onset dystonias have mixed disorders of tone, which can include spasticity, myoclonus, choreoathetosis, and hypotonia in addition to dystonia. This makes assessing outcomes a significant clinical challenge. Most centers rely on the Burke-Fahn-Marsden [40, 41] and/or Barry Albright Dystonia [42] scales as the primary outcome measures. Neither of these is designed for mixed disorders of tone and has limited applicability in the pediatric population. Pediatric dyskinesia has been introduced as an alternative [43]. Attempts have been made to capture less measurable changes in status using neuropsychological and/or quality of life measures, but again there are difficulties applying these in a uniform measure when motor impairment may be accompanied by language limitations with or without intellectual impairment.

There is little disagreement that DBS is an appropriate intervention for many primary genetic dystonias with intact brain anatomy. It is also recognized that even in this population, there are non-responders. Alternate targets may provide the answer for some of these patients. Disorders involving dystonia with other movement disorders or comorbidities are even more complex. DBS may be part of the treatment paradigm.

Better assessment tools are needed to measure the relative contribution and response to treatment of the various components in mixed movement disorders both genetic (e.g., ataxia telangiectasia, spinocerebellar ataxias) and acquired (cerebral palsy, acquired brain injury).

There are some disorders and interventions that are not amenable to traditionally accepted prospective blinded trials. This may be due to the rarity and severity of the disorder, or relate to the intervention itself [44]. In the case of DBS, sham surgery is simply not a viable ethical option. The time lag to DBS may be month to even years in dystonia, making outcomes assessment difficult. To this end, registries are emerging as a useful tool for aggregating data. The number of pediatric patients undergoing DBS remains relatively small. Pediatric implantation requires a special team of physicians, therapists, and support staff. Even the largest and most experienced centers implant a few patients annually. For this and many other reasons, data sharing between centers is important to improving our understanding of and patient outcomes from DBS surgery. To that end, we have developed an international registry of pediatric patients undergoing DBS [45•].

Conclusions

Deep brain stimulation continues to evolve as a treatment for medically refractory dystonia due to a wide variety of etiologies in children. Refinements in surgical technique have made the procedure more tolerable. There is still much to be learned

about optimal and secondary targets for treatment. With the move away from intraoperative recordings, newer techniques are being developed to help elucidate the pathophysiology of dystonia in various disorders. Due to the rarity of these disorders and the limited number of centers performing DBS on children, data sharing will be a vital part of the shared learning experience needed to enhance patient care. After working through the complex legal, compliance and regulatory hurdles of international data sharing, the international pediatric deep brain stimulation registry is now open for participation. Information is available at www.PEDiDBS.org.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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45.• Marks W, Bailey L, Sanger TD. PEDiDBS: The pediatric international deep brain stimulation registry project. Eur J Paediatr Neurol. 2017;21(1):218–22. https://doi.org/10.1016/j.ejpn.2016.06.002. **This article highlights the need and introduces a mechanism for data sharing across centers performing DBS on pediatric patients.**