REVIEW

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Deep brain stimulation in pediatric dystonia: a systematic review

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Abstract

While deep brain stimulation (DBS) treatment is relatively rare in children, it may have a role in dystonia to reduce motor symptoms and disability. Pediatric DBS studies are sparse and limited by small sample size, and thus, outcomes are poorly understood. Thus, we performed a systematic review of the literature including studies of DBS for pediatric (age < 21) dystonia. Patient demographics, disease causes and characteristics, motor scores, and disability scores were recorded at baseline and at last post-operative follow-up. We identified 19 studies reporting DBS outcomes in 76 children with dystonia. Age at surgery was 13.8 ± 3.9 (mean ± SD) years, and 58% of individuals were male. Post-operative follow-up duration was 2.8 ± 2.8 years. Sixty-eight percent of patients had primary dystonia (PD), of whom 56% had a pathological mutation in DYT1 (DYT1+). Across all patients, regardless of dystonia type, $43.8 \pm 36\%$ improvement was seen in Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor (-M) scores after DBS, while $43.7 \pm 31\%$ improvement was observed in BFMDRS disability (-D) scores. Patients with PD were more likely to experience $\geq 50\%$ improvement (56%) in BFMDRS-M scores compared to patients with secondary causes of dystonia (21%, $p = 0.004$). DYT1+ patients were more likely to achieve $\geq 50\%$ improvement (65%) in BFMDRS-D than DTY1− individuals (29%, $p = 0.02$), although there was no difference in BFMDRS-M $\geq 50\%$ improvement rates between DYT1+ (66%) or DYT1− (43%) children ($p = 0.11$). While DBS is less common in pediatric patients, individuals with severe dystonia may receive worthwhile benefit with neuromodulation treatment.

Keywords Deep brain stimulation · Dystonia · Pediatrics · Functional neurosurgery · Pediatric neurosurgery

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Introduction

Deep brain stimulation (DBS) is a powerful neurosurgical technique that has been used in the treatment of a myriad of pathologies including Parkinson's disease [21], tremor [3], obsessive-compulsive disorder [5], depression [35], Tourette syndrome [43], pain [44], obesity [10], disorders of consciousness [16], vocal tremor [18], and traumatic brain injury [45], among others. Over the last several decades, the capabilities of DBS have expanded rapidly with technological innovations, surgeon experience, and scientific discoveries. Despite these advances, pediatric-specific randomized controlled trials and large case series using DBS have not yet been reported for any indication. Precise diagnosis of dystonia etiology (genetic or otherwise) remains a challenge; there is a lack of consensus on treatment approach, and there are significant barriers to performing robust multi-institutional studies.

Dystonia is a debilitating neurological condition with prevalence of 15 to 30 cases per 1,000,000 people [42]. There are many causes of dystonia—including primary causes, most often due to genetic mutation [7, 28]. Primary generalized

dystonia (PD) can present at any age, with those patients diagnosed earlier in life (before age 26) likely to experience more severe disease [42]. Although medications remain first-line therapy for symptom amelioration, the options are limited, and evaluating response to therapy is further challenged by developmental, behavioral, and speech delays that are often comorbid in the pediatric patient population. Intrathecal baclofen and botulinum toxin injections can be useful for treating dystonia, but outcomes are variable, particularly with regard to upper extremity symptoms [8, 32, 39]. Furthermore, dystonia is often progressive and not curative through pharmacological therapies, increasing the complexity of treating these patients. Thus, surgical approaches to treating pediatric dystonia may offer the only disease-altering course of treatment.

Secondary causes of dystonia are highly variable and consist of many pathologies. DBS has been widely reported in children with movement disorders [29], with primary causes of dystonia being the most commonly treated [2], although a broad range of pathologies have been treated with DBS. However, DBS treatment guidelines for pediatric patients with dystonia are not well-established. Similarly, even among patients carrying the same genetic mutation causing primary dystonia, symptom severity and response to medications is highly variable. Primary cases of dystonia have largely been diagnosed by genetic testing and have been most frequently treated with DBS compared to secondary etiologies of dystonia [31]. However, there is no consensus on specific recommendations regarding when, if at all, DBS should be performed and for patients with various causes of dystonia.

The specific challenges involved in treating children with these complex disorders are numerous. While grading systems of symptom and movement severity, such as the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDS), have been used, there are no standardized recommendations for thresholds that must be met to warrant surgical intervention [4]. Development of future grading systems for pediatric dystonia should make every effort to limit observer bias and prioritize objectivity as many comorbid conditions make clinical evaluation difficult. Thus, improved diagnostic and treatment paradigms for these patients are needed, and DBS represents an attractive option for pediatric patients with dystonia. In general, studies of DBS for dystonia in children are sparse and limited by small sample size, and thus, indications and outcomes are poorly understood. There is also significant variability in outcomes for patients with primary vs. secondary causes of dystonia, further delineating the need for improved disease classification and response to DBS. However, patients that respond to DBS experience a significant improvement in his/her quality of life despite being unable to correct the underlying causes of disease. It may therefore be useful to systematically summarize the limited data that are currently available in the literature, to help identify questions requiring further study. Here, we present the first systematic review of DBS outcomes in children with dystonia.

Materials and methods

Literature search

PubMed was searched in March 2018 according to PRISMA guidelines for systematic reviews (Fig. 1). The search terms included "("dystonia" OR "movement disorder" AND "deep brain stimulation" AND ("children" or "pediatric" or "adolescent"))." This query resulted in 263 articles. Inclusion criteria included (1) peer-reviewed publications from 1980 through March 2018 and (2) studies containing one or more pediatric patient ($\leq$ 21 years of age) treated with deep brain stimulation for dystonia. Exclusion criteria included (1) non-English articles, (2) review or surgical technique articles, and (3) articles in which individual pediatric patient data could not be extracted. Titles and abstracts were then reviewed for inclusion. Review articles were intentionally excluded from our analysis so that only quantitative outcomes studies, rather than qualitative information, could be aggregated. In addition, this article is the first to aggregate DBS surgical outcomes data in pediatric patients with movement disorders, although there have been a number of articles reporting qualitative information describing the utility of DBS. If exclusion was not confirmed based on the title and abstract, the full text was reviewed. In total, 19 articles met all criteria and were reviewed in their entirety (Table 1). This study was registered with PROSPERO, the international prospective register of systematic reviews (https://www.crd.york.ac.uk/prospero/).

Data extraction

The following information was extracted from the included studies by M.A.M. and confirmed independently by A.T.H. and D.J.E.: (1) age at onset (< 18 years); (2) age at surgery (<
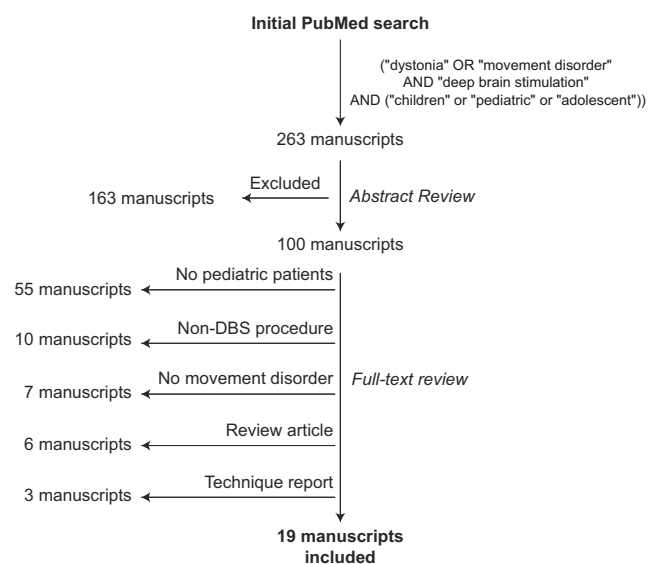

Fig. 1 PRISMA outline for systematic review

Table 1 Patient characteristics

	Data	% data available
Age (years)		
At diagnosis	6.91 ± 0.47	82
At surgery	13.8 ± 0.45	100
Duration of illness (years)	6.4 ± 0.44	82
Sex		87
Female	24 (32%)	
Male	44 (58%)	
Etiology		100
Primary dystonia		
DYT1+	29 (38%)	
DYT1−	23 (30%)	
Secondary dystonia	24 (32%)	
BFMDRS		
Pre-op motor	60.4 ± 2.88	100
Post-op motor	35.9 ± 3.20	100
Pre-op disability	15.2 ± 1.14	47
Post-op disability	8.83 ± 1.08	47
DBS target	76	100

Data are *n* (%) for counts or mean ± SD for continuous variables. % data available indicates the percentage of reports with each variable reported

21 years); (3) duration of illness before surgery; (4) sex; (5) etiology of dystonia, including genetic testing; (6) anatomical target for DBS; (7) pre- and post-operative Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor (BFMDRS-M) and (BFMDRS-D) disability scores; and (8) length of follow-up after surgery. Only pediatric data that could be disaggregated from adult data was included in this study. All patients were diagnosed before age 18 and were thus considered pediatric cases. Variables were selected based on the availability within individual texts suitable for quantitative outcomes analysis. Individual patient data are provided in Supplemental Materials, online.

Statistics

Chi-square was used to relate etiology of dystonia to < 50% vs ≥ 50% improvement in BFMDRS-M and BFMDRS-D after surgery. We chose to report the data as greater than 50% improvement (using the chi-squared test) since there are no standardized indications for operative intervention based on BFMDRS scores. Furthermore, based on the synthesis of our review of the literature, many consider greater than 50% improvement to be clinically significant. Univariate logistic regression was used to relate age, gender, or duration of symptoms to improvement in BFMDRS-M and BFMDRS-D. Unpaired, two-way, Student's *t* test was performed to relate percent change in BFMDRS-M and BFMDRS-D to etiology of dystonia. These statistics were performed for summary

purposes only, as insufficient data were available in the literature for formal meta-analysis.

Results

Demographics

We performed a systematic review of DBS outcomes in the treatment of dystonia in children. All included studies and individual patient characteristics are listed in Supplemental Materials, online. Overall, we identified 19 studies including 76 patients (58% male) reporting DBS outcomes for dystonia in children. The mean age at surgery was 13.8 ± 3.9 (mean ± SD) years. Duration of time between onset of symptoms and surgery was 6.4 ± 3.5 years, and post-operative follow-up was 2.8 ± 2.8 years, with 78% of patients having more than 1 year of follow-up. All studies were retrospective, and no prospective studies or trials were reported. Summary data are listed in Table 1.

Dystonia etiology

Primary generalized dystonia (PD) was the most common form of dystonia reported (68%) while other causes of dystonia—including secondary generalized and focal dystonia—were reported in 32% of children. Causes of PD included mutations in torsin family 1 member A (DYT1+), the most common genetic cause of dystonia [47], or patients with PD and no known pathological mutation in DYT1 (DTY1−). Due to the limited number of reports and inconsistencies in reporting body part–specific distribution patterns of dystonia, we are unable to complete this subtype analysis on this current cohort of patients. Causes of secondary dystonia included cerebral palsy of unknown etiology (*n* = 7), primal focal/segmental dystonia (*n* = 5), secondary generalized dystonia of unknown etiology (*n* = 2), dystonic cerebral palsy due to hyperbilirubinemia (*n* = 2), dystonic cerebral palsy due to hypoxic-ischemic encephalopathy (*n* = 2), dystonia due to traumatic brain injury (*n* = 1), basal ganglia calcifications (*n* = 1), dystonic cerebral palsy due to meningitis (*n* = 1), intracerebral hemorrhage (*n* = 1), Hallervorden-Spatz disease (*n* = 1, secondary due to iron accumulation), axonal brain injury (*n* = 1), encephalopathy (*n* = 1), and kernicterus (*n* = 1). Since there was such heterogeneity reported in the literature on secondary causes and quantitative outcomes information (i.e., Burke-Fahn-Marsden Dystonia Rating Scale) was sparsely reported, we chose to treat all secondary causes as one category. The symptoms most reported in the literature as indications for DBS included dystonic or "stiff" movement as well as "abnormal movements." However, these data were sparsely reported in cases where the diagnosis was not PD. Further classifying qualitative symptom improvement in

pediatric patients with dystonia may be difficult due to comorbid developmental delay. Thus, our focus here was to provide a quantitative assessment of motor and disability scores that could later be expanded as additional information becomes available.

DBS treatment

Ninety-one percent of individuals were implanted with a bilateral globus pallidus interna (GPi) target, one (1.3%) patient received a unilateral GPi implant, one (1.3%) individual received bilateral GPi plus subthalamic nucleus (STN), and five (6.6%) children received a unilateral GPi implant and a contralateral GPi lesion. Thus, we only considered surgical interventions targeting the GPi. Across all patients with data available, BFMDRS-M scores improved by $43.8 \pm 36\%$ (mean ± SD) after surgery, with 45% of individuals achieving ≥ 50% improvement, while BFMDRS-D scores improved by $43.7 \pm 31\%$ post-operatively, with 47% of children achieving ≥ 50% improvement. Patients with PD (56%) were more likely to experience > 50% improvement in BFMDRS-M scores after surgery compared to patients with other causes of dystonia (21%, $p = 0.004$, chi-square), as shown in Fig. 1. Improvement in BFMDRS-D scores after surgery could not be compared in primary vs. secondary dystonia, as post-operative scores were only reported in two patients with secondary dystonia. Among individuals with PD, there was no difference in the likelihood of achieving ≥ 50% improvement in BFMDRS-M scores between patients with DYT1+ (66%) versus DYT1− (52%) disease ($p = 0.11$, chi-square), although DYT1+ patients were more likely (65%) to achieve ≥ 50% improvement in BFMDRS-D than DTY1− individuals (29%, $p = 0.02$, chi-square), as shown in Figs. 2 and 3. Additional genetic causes of dystonia could not be investigated here due to limited reporting in the literature. Age, gender, duration of symptoms, and length of follow-up were not found to be predictive of BFMDRS-M or BFMDRS-D outcomes ($p > 0.05$ for each, logistic regression). Study limitations are listed in Table 2.
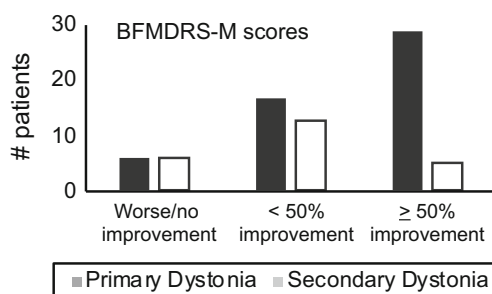

Fig. 2 Pediatric patients with primary dystonia (PD) were more likely to experience ≥ 50% improvement in Burke-Fahn-Marsden Dystonia Rating Scale motor component (BFMDRS-M) after DBS than patients with secondary causes of dystonia ($p = 0.01$, chi-square)
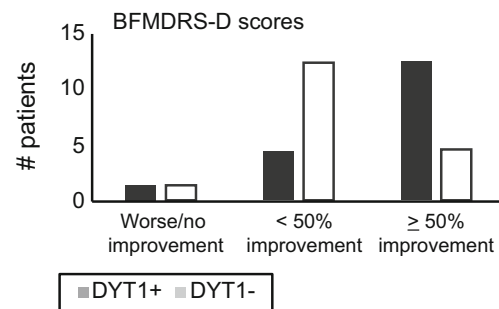

Fig. 3 Patients with primary generalized dystonia who carry a DYT1 mutation (DYT1+) were more likely to experience ≥ 50% improvement in BFMDRS-D scores compared to patients without the mutation (DYT1−) ($p = 0.02$, chi-square)

Discussion

We performed the first systematic review of DBS outcomes in the treatment of pediatric patients with movement disorders, including primary generalized dystonia and secondary causes of dystonia. Our results suggest that DBS can be an efficacious treatment in patients with dystonia, but patients with PD may be more likely to experience greater improvement in motor symptoms than those with secondary dystonia. Among PD patients, those who are DYT1+ may be more likely to experience an improvement in disability scores compared to patients who are DYT1−. Thus, it is possible that a known genetic etiology of dystonia portends a more favorable DBS outcome. While our analysis is limited by a small number of reported cases in the literature, this report serves as a proof-of-principle that DBS may be effective in children with dystonia. Furthermore, we are the first, to our knowledge, to aggregate quantitative outcomes data for DBS treatment of pediatric dystonia. However, larger prospective studies and/or a centralized patient registry, such as the Pediatric International Deep Brain Stimulation Registry Project (PEDiDBS) [30], is needed to evaluate outcomes in greater detail.

All patients were described as poorly responsive or refractory to medical therapy for dystonia and failed medication trials of anticholinergic drugs, benzodiazepine derivatives, botulinum toxin injections, neuroleptics, oral baclofen, and/or intrathecal baclofen. Overall, patients experienced symptoms for 6.4 ± 3.5 years prior to DBS treatment. The number and order of medications attempted prior to DBS placement were not reported in any of the studies included in our review. Comparisons of pre-operative and post-operative medication regimens were scarce, though several studies reported substantial decrease in the amount and variety of daily maintenance medications after DBS placement [25, 46, 51].

The primary scoring system used to assess pre-operative severity as well as post-operative improvement in patients with dystonia is the BFMDRS, as described by Albanese et al. [1]. This rating scale takes into account both motor and overall

Table 2 Studies included in our analysis detailing number of pediatric patients with individual data, level of evidence, and potential biases (< 5 patients, mixed adult and pediatric population, adolescents only, young children only, follow-up length)

Study	Number of patients	Study features
Cersosimo et al. [6]	7	Mixed population, variable long-term follow-up (1.2–7.7 years)
Ghosh et al. [13]	8	Adolescents only
Goto et al. [15]	2	< 5 patients, limited follow-up length (1 year)
Jin et al. [19]	1	Case report, young child
Keen et al. [22]	5	Mixed population, variable follow-up (0.16–3.50 years)
Krause et al. [23]	4	Mixed population (age and etiology), variable follow-up length (1–5.5 years)
Krause et al. [24]	1	Mixed population (only 1 patient met inclusion criteria)
Krause et al. [25]	6	Adolescents only
Kupsch et al. [26]	1	Case report, patient age not disclosed
Mehrkens et al. [33]	4	Mixed population
Miyagi et al. [36]	2	< 5 patients, young children only
Olaya et al. [37]	1	Limited long-term follow up (all less than 1 year)
Oterdoom et al. [38]	1	Case report, rare genetic mutation
Parr et al. [40]	4	< 5 patients, very young children < 2 years old
Petrossian et al. [41]	13	Mixed population, mixed etiology
Starr et al. [46]	1	Mixed population, sex unknown, mixed etiologies
Tronnier et al. [48]	1	< 5 patients, 1 pediatric patient
Vidailhet et al. [49]	5	Mixed population, limited to 1-year follow-up
Zorzi et al. [51]	9	Mixed population, variable follow-up (0.16–4.17 years)

disability measures and has been demonstrated to be a relatively reliable tool for estimating severity of disease, but it is not the only method to quantify movement disorder outcomes [14]. However, the BFMDRS is not pediatric-specific, thereby limiting its use in clinically evaluating pediatric patients with dystonia. Thus, while some level of functional outcome can be captured using BFMDRS, it is worth considering whether additional scoring systems should be developed to better reflect the specific features seen in pediatric cases of dystonia.

Previous reviews on DBS in children have focused on general indications [9, 27], surgical technique [46], qualitative assessment of movement disorder [2, 11, 31], and the value of genetic testing in patient selection for DBS [20]. Prior pediatric-specific reviews of DBS treatment for movement disorders have focused on single-center experiences, surgical techniques specific to children, and descriptions of illustrative cases [2, 9, 11, 20, 27, 31, 46]. However, no quantitative analysis of pediatric-specific outcomes after DBS has been performed, to our knowledge. Given the surprisingly low number of articles that met our inclusion criteria, additional quantitative studies in pediatric DBS need to be performed. Previous qualitative reviews have described that DYT1+ patients may be more likely to respond to DBS treatment than individuals with heterogeneous causes of secondary dystonia [2, 31], which is supported by our present findings. Thus, the quantitative results presented here are mostly in agreement with prior qualitative reviews on this topic.

Although DYT1+ patients experienced more favorable outcomes, DYT1 is not the only genetic cause of primary dystonia. Complex and myoclonic dystonias can result from mutations in PKAN, among other monogenic causes. However, genetic testing for many of these disorders is not routinely used and reported in the literature. Various groups have reported remarkably diverse genetic etiologies underlying physical manifestations of dystonia in children and adults [12, 17, 34, 50]. While surgical management of these patients may improve functional outcomes, molecular and systems-based analysis of known and unknown genetic drivers of movement disorders are needed to better understand disease pathophysiology. Importantly, as gene-sequencing and "personalized medicine" approaches may become more mainstream, more selective genetic criteria may be elucidated to select for patients who would most likely benefit from DBS. While the field is not currently primed for this level of granularity, it is worth considering the potential genomics may play in guiding the treatment of dystonia and other neurological disorders. The potential to identify younger patients with dystonia likely to benefit from surgery, based on genetic criteria, may be worthwhile.

Secondary causes of pediatric dystonia are highly variable and reflected in the current aggregation of the literature. While there are clear pathophysiological mechanisms responsible for driving PGD, such as mutations in DYT1, secondary causes of dystonia can occur without antecedent genetic causes.

Thus, it could be surmised that amelioration of associated dystonia symptoms in patients with secondary dystonia may improve quality of life. However, secondary dystonia is associated with many genetic conditions that are not mediated by DYT1, such as inborn errors of metabolism, vitamin deficiencies, and neurodevelopmental conditions. Therefore, treatment strategies have been focused on reversing the underlying cause of the dystonia symptoms. Our data imply that use of DBS may provide some symptomatic benefit for these patients, despite the inability to permanently reverse the underlying cause of the disease. However, additional studies are needed to delineate the degree to which DBS can ameliorate dystonic symptoms due to secondary causes.

Standardized surgical indications and treatment of pediatric dystonia would represent a major leap forward for the field. While additional well-controlled, multi-center studies are needed to delineate optimal treatment practices, preliminary data suggests that pediatric patients with varying forms of dystonia could benefit from DBS. We hope this review serves as a springboard for discussion of expanding the use of DBS in pediatric dystonia, providing an unmet therapeutic need to this patient population.

Limitations and conclusions

Our study has several important limitations to consider. All studies examined were retrospective, mostly mixed population, and with variable follow-up have been reported, limiting data quality (Table 2). Furthermore, the studies are all small and many are not restricted to the pediatric population. All data here was extracted from mixed-population studies and was presented here only when the pediatric-specific information could be disaggregated. Publication bias may also lead to selective reporting of more favorable outcomes limiting accurate assessment of outcomes in this patient population. Finally, univariate statistics are provided here for summary purposes only, as insufficient data are available for formal meta-analysis in this field. Nonetheless, our study is the first, to our knowledge, to systematically examine the available literature of DBS for pediatric dystonia, providing *quantitative* outcomes data. We conclude that DBS may be effective in improving motor symptoms and degree of disability in this disorder. Outcomes may be more favorable in PD than secondary dystonia, and among PD patients, in DYT+ patients compared to those who are DYT−. Larger, prospective studies will be important to further evaluate long-term outcome rates and predictors in this field. We hope our review serves as a useful summary of how future data should be presented in order to aggregate data across multiple studies and centers.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical approval No medical records were accessed in completing this article, and only previously approved, published studies were included in our analysis. Thus, institutional review board approval was required.

Informed consent Only published studies were used for our analysis, and no patient medical records were accessed in completing this article. Thus, patients' consent was not required.

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