ORIGINAL ARTICLE

Deep brain stimulation in pediatric dystonia: calls for therapeutic realism over nihilism

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Abstract

Purpose Pediatric dystonia (PD) has a significant negative impact on the growth and development of the child. This study was done retrospectively to analyze functional outcomes in pediatric patients with dystonia who underwent deep brain stimulation.

Methods In this retrospective analytical study, all the patients of age less than 18 years undergoing deep brain stimulation (DBS) for dystonia between 2012 and 2020 in a single center were analyzed and their functional outcomes were measured by the Burke–Fahn–Marsden-dystonia-rating-scale (BFMDRS).

Results A total of 10 pediatric patients were included with a mean age of onset, duration of disease, and age at surgery being 5.75 years, 7.36 years, and 13.11 years, respectively, with a mean follow-up of 23.22 months. The mean pre-DBS motor score was 75.44 ± 23.53 which improved significantly at 6-month and 12-month follow-up to 57.27 (p value 0.004) and 50.38 (p value < 0.001), respectively. Limbs sub-scores improved significantly at both the scheduled intervals. There was a significant improvement in disability at 1-year follow-up with significant improvement in feeding, dressing, and walking components. There was a 27.34% and 36.64% improvement in dystonia with a 17.37% and 28.86% reduction in disability at 6 months and 12 months, respectively. There was a positive correlation between the absolute reduction of the motor score and improvement in disability of the patients at 6 months (rho = 0.865, p value 0.003).

Conclusions DBS in PD has an enormous role in reducing disease burden and achieving a sustainable therapeutic goal.

Keywords Pediatric dystonia · Deep brain stimulation · DBS · Surgery

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Introduction

Pediatric dystonia has a significant negative impact on the growth and development of the child, and their access to education and activity, causing significant disability, deformity, and rarely death [1, 2]. It is a spectrum of disorders that includes persistent debilitating clinical conditions with a significant effect on the patient and caretaker's quality of life [3]. Dystonia is one of the most common types of movement disorders and is typically defined as the movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both [4]. In the pediatric age group, dystonia more often tends to be generalized as compared with adult-onset dystonia [5].

The basic pathophysiology of dystonia is poorly understood [6]. But rarely does one model fit all [7, 8]. The recently proposed network model comprehensively accommodates pathological and radiological evidence of dystonia

being associated with abnormalities in multiple different brain regions. Various defects in sensorimotor integration, neural inhibitory processes, and maladaptive plasticity are proposed to be central elements in the occurrence of dystonia [9].

In line with revolutionary progress in medical science, the emergence of deep brain stimulation (DBS), as a treatment option for dystonia, has given hope and a chance for better disease control for the patients and families who are dissatisfied with medical management and the psychosocial impact of the disease itself [5, 10]. In contrast to traditional ablative procedures, DBS has various advantages which include far fewer adverse effects and complications, the fundamental scope of reversibility and programmability of the stimulation tailored to the need of the patients, and potential long-term sustainable and achievable therapeutic goals [11].

DBS was initially introduced by F. Mundinger in 1977 as a novel option for treating spasmodic torticollis [12]. After this breakthrough, the US Food and Drug Administrator (FDA) gave its approval for its use in tremors (1997) and Parkinson's disease (2001) [13, 14]. In the year of 1996, an 8-year-old girl child became the first pediatric patient to receive bilateral Globus Pallidus Interna (GPi) DBS and she showed effective results twenty years after the surgery [15, 16]. Finally, in 2003, FDA gave humanitarian device exemption for drug-resistant dystonia in children of age seven or more. Since then DBS has been at the forefront in carefully selected patients of pediatric dystonia [17–20].

There is a scarcity of data in the published literature regarding outcomes of pediatric dystonia patients following DBS [19, 21–38] (Table 1). In our study, we have retrospectively analyzed our results in pediatric patients with dystonia who underwent deep brain stimulation and discussed our findings in light of existing literature. To the best of our knowledge, this is the second-largest series in the world on pediatric dystonia.

Methods

This is a retrospective analytical study of pediatric patients who underwent deep brain stimulation for dystonia between 2012 and 2020 at a tertiary care hospital in India. All the patients of age less than 18 years with failed medical management undergoing DBS for dystonia were included in the study. Their medical records were accessed from the hospital medical records, and radiological images (MRI) were reviewed from hospital PACS.

Clinical evaluation and outcomes measures

After the failure of an adequate medical trial, patients were advised for DBS. After a multidisciplinary team discussion, only those patients without any contraindications were considered for DBS after obtaining written informed consent. All the patients included in the study underwent thorough neurological evaluation and video recording by two independent expert neurologists. Pre-op baseline functional status of the patients was assessed by Burke–Fahn–Marsden dystonia rating scale (BFMDRS) and their movement (M) and disability (D) sub-scores were calculated. The BFMDRS-M score (range, 0–120) is the sum of 9 body region sub-scores, which were grouped into 4 anatomical areas: face (eyes and mouth), speech and swallowing (SS), axial (neck and trunk) segment, and limbs. The total BFMDRS-D score (range, 0–30) is the sum of individual ratings for 7 activities: speech, handwriting, and the degree of dependence concerning hygiene, dressing, feeding, swallowing, and walking. Higher scores indicate worse motor impairment and disability. The same scoring was repeated at 6 months and 12 months post-op. In the postoperative period, all the scoring and evaluations were done on-state at the scheduled interval.

Neurosurgical procedure and deep brain stimulation programming

All the cases included in our study underwent DBS by a single surgeon (DS). All patients underwent frame-based MRI and microelectrode-guided stereotactic implantation of the leads (model 3389; Medtronic Inc, Minneapolis, MN). A preoperative MRI was done for all patients to locate the targets (GPi, STN, and VOP). After obtaining written informed consent for surgery, they underwent implantation of a quadripolar electrode (Medtronic, Minneapolis) in the targets under local/general anesthesia. The intraoperative targets were refined and tailored by neurophysiological monitoring. A Multitrack pentapolar micro-drive recording system (FHC, Medtronic) was used for this purpose. A standard assessment of three microelectrode tracks (anterior, posterior, and medial) in the sagittal plane was used for all cases. Postoperative imaging (CT/MRI) was performed to confirm the accurate placement of electrodes. All these patients underwent immediate postoperative brain imaging (CT/MRI), which was fused with the preoperative images to confirm the accuracy of electrode placement (Fig. 1A–F). Standard protocols were followed while doing the initial programming. All the contacts were tested in a monopolar fashion. Once the best contact was identified (which is usually having the highest threshold for side effects and the lowest threshold for the target clinical response), a fine augmentation of voltage could be achieved up to 4 V. The ventral-most contacts were preferred for therapy in most of the cases. When the response was unsatisfactory, we gradually increased the pulse width to the sub-threshold

Table 1 Review of literature of DBS in pediatric dystonia

	Number of patients	Average age at onset (years)	Age at surgery	Genetic status	Type of dystonia	Pre-op BFMDRS-M score (motor score)	Post-op BFMDRS-M score (motor score)	Pre-op BFMDRS-D score (disability score)	Post-op BFMDRS-D (disability) score	Length of follow-up (years)	Surgery
Cersosimo et al. (2008) [21]	7 (2 males, 5 females)	8.5	14.5	DYT1 +—6 NA -1	PGD	59	29.7	18.1	11.4	4.9	
Ghosh et al. (2012) [22]	8 (NA)	7.5	14.1	DYT1 +2 DYT1 -4 NA—2	PGD 5 SHD 1 SGD 1 PSD 1	NA	NA	NA	NA	4.6	
Goto et al. (2006) [23]	2 (males 2)	8	18	DYT1+2	PGD 2	65.2	1.5	5	6.5	1	
Jin et al. (2012) [24]	1 (females 1)	2	7	DYT1+	PGD	34	3	11	3	1	
Keen et al. (2014) [25]	5 (males 4 females 1)	3.4	11.4	-	Dystonic CP -4 ICH -1	74.9	52.4	NR	NR	2.2 years	
Krause et al. (2015) [38]	13 (8 males, 5 females)	7.8	15.3	DYT1+8 DYT6+1	PGD 7 HTD 2 STD 1 HS 1 IGD 2	56	27.1	15.5	4.4	6.05	
Kupsch et al. (2003) [28]	1	10	17	DYT1+	PGD	34.5	27	NR	NR	NR	B/L GPi DBS
Mehrkens et al. (2010) [29]	5 (sex NR)	9.1	13	DYT1+3 DYT1-2	PGD 5	NR	NR	NR	NR	3	
Miyagi et al. (2013) [30]	2 (males 1, females 1)	9	10	DYT1+2	PGD 2	60	76	NR	NR	5	
Olaya et al. (2013) [19]	9 (sex NR)	NR	16.3	NR	CP 6 Kernicterus 1 Axonal injury 1	111.5	90.5	NR	NR	0.3	
Oterdoom et al. (2018) [31]	1 (males 1)	3.5	9	DYT6 (THAP1)	PGD	71	64	26	15	3	B/L GPi DBS
Parr et al. (2007) [32]	4 (males 2, females 2)	5.1	12	DYT1+1 DYT1-3 DYT6 1	PGD	82.75	34	19	12.8	1.6	
Petrossian et al. (2013) [33]	13 (10 males 3 females)	9.7	13.7	DYT1+3 DYT1-8 PANK2+2	PGD 8 SGD 2 PF 3	39.8	22.23	NR	NR	4.2	

Table 1 (continued)

	Number of patients	Average age at onset (years)	Age at surgery	Genetic status	Type of dystonia	Pre-op BFMDRS-M score (motor score)	Post-op BFMDRS-M score (motor score)	Pre-op BFMDRS-D score (disability score)	Post-op BFMDRS-D (disability score)	Length of follow-up (years)	Surgery
Starr et al. (2004) [34]	7 (sex NR)	16.14	NR	*DYT1 + 5* *NR 2*	PGD 4 PSD 2 CP 1	64.4	29	NR	NR	1.1	
Trommier et al. (2000) [35]	1 (sex NR)	10	13	*DYT1 +*	PGD	77	50.5	NR	NR	0.5	B/L GPi DBS
Vidailhet et al. (2005) [36]	5 (2 males 3 females)	7.4	17.2	*DYT1 + 1* *DYT1 - 4*	PGD 5	38.4	17.2	9	4.2	1	
Zorzi et al. (2005) [37]	9 (7 males, 2 females)	3.5	11.7	*DYT1 + 0* *DYT1 - 7* *Unknown 2*	PGD 7 Basal ganglia calcification 1 Encephalopathy of unknown origin 1	65.8	40.3	16.6	11.5	1.2	

B/L GPi bilateral internal globus pallidus, *CP* cerebral palsy, *GDD* global developmental delay, *HS* Hallervorden-Spatz, *HTD* hereditary torsion dystonia, *HB* hyperbilirubinemia, *HIE* hypoxic-ischemic encephalopathy, *IGD* idiopathic generalized dystonia, *PF* primary focal, *PGD* primary generalized dystonia, *PSD* primary segmental dystonia, *SGD* secondary generalized dystonia, *SHD* secondary hemidystonia, *STD* sporadic torsion dystonia, *STN* substantia nigra, *THAP1/DYT6* THAP domain containing 1, *DYT1/TOR1A* torsion family 1 member A, *U/L GPi* unilateral internal globus pallidus, *NR* not-reported
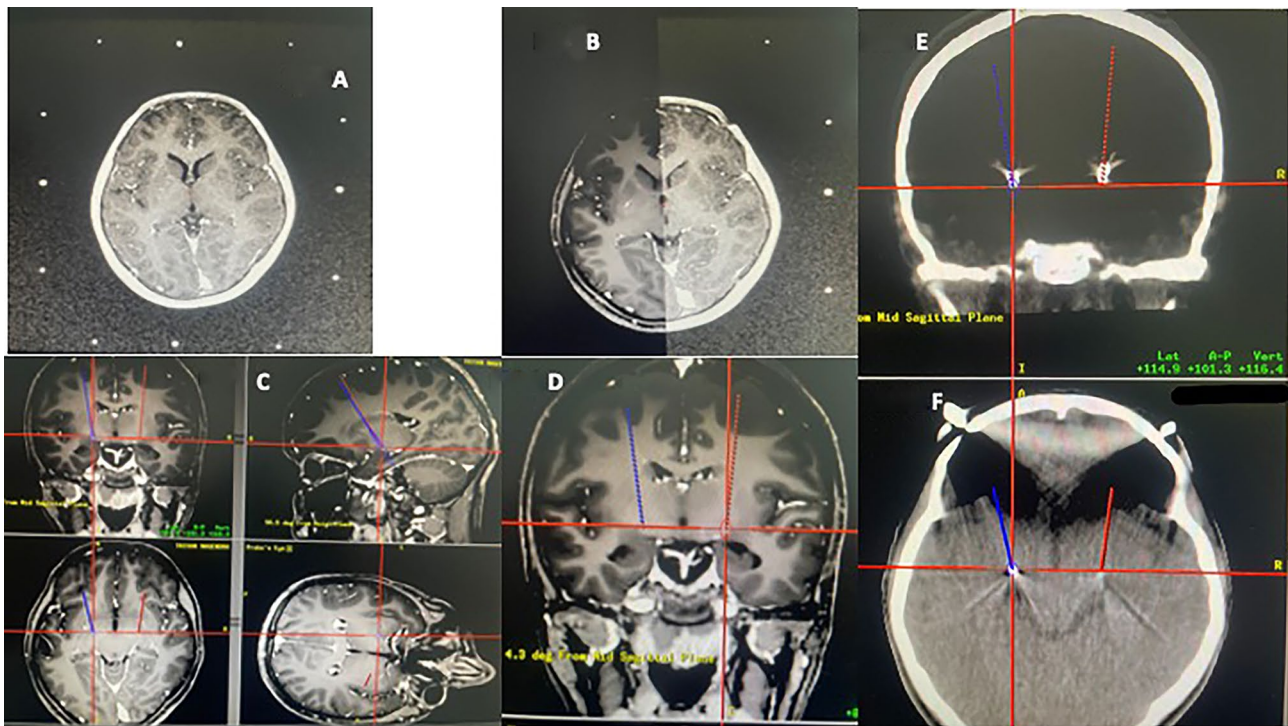
Fig. 1 Imaging of planning the target on the planning system. **A** Navigation protocol MRI (T1-weighted post-contrast 1.5 T) with the frame on the day of the surgery. This is used as the registration series. **B** The fusion between the 2 MRI sequences (left — T1-weighted post-contrast 3 T and right T1-weighted post-contrast 1.5 T). The 3 T sequences are used for direct planning as the anatomy is better defined. 1.5 T images used as registration image due to it being more accurate due to lesser distortion. **C**, **D** The virtual trajectory planning on the MRI images. **E** and **F** The post-operative CT scan fused with the preoperative images to check the accuracy of the lead placement

of adverse effects level. After all these adjustments, if the responses were still suboptimal, the next contiguous contact (usually more dorsal) was used. The same sequential methods were followed for them as well. During scheduled follow-ups, all the patients were examined for hardware-related issues [39–41].

Statistical analysis

The retrospective data were retrieved and tabulated in an Excel sheet. The collected data were analyzed in SPSS V28.0.0.0. Descriptive statistics of the quantitative data were described as mean, standard deviation, and range, and those of the nominal data were described as frequency and percentage. Analysis of longitudinal data was done using repeated-measures ANOVA; sphericity assumption was tested using Mauchly's sphericity test. The pair-wise correlation was done using Bonferroni correction. The effect size of each test was tabulated as partial eta-squared. Correlation testing was conducted using Spearman's rank correlation. A p value less than 0.05 was considered statistically significant.

Data sharing

Data that support the findings of this study are available upon request to the corresponding author.

Results

A total of 10 pediatric patients (8 males, 2 females) (Table 2) underwent DBS for the above-mentioned pathology and all were included in the study. Among them, the majority of the patient underwent bilateral GPi-DBS (#Case 1, #Case 2, #Case 4, #Case 6, #Case 7, #Case 8, #Case 9, #Case 10), one patient underwent B/L STN and GPi DBS (#Case 3), and one patient underwent left STN and VOP DBS (#Case 5). Patients were decided for surgical management only after failure of a trial of adequate medical management, including anticholinergics, benzodiazepines, neuroleptics, baclofen, and botulinum toxin injections. All patients included in the study had a severe disability with normal cognitive functioning and psychiatric profile as assessed by neurologists and

Table 2 Clinical and demographic details of all the patients included in the study

Serial no	Diagnosis	Age at onset (years)	Age at presentation (years)	Age at surgery (years)	Duration of disease (years)	Sex	DBS target	Follow-up duration (months)	Motor score Pre-DBS	6 months	12 months	Disability score Pre-DBS	6 months	12 months	Clinical feature	Complications
Case 1	Dystonia-NBIA	4	4.5	6	2	Female	B/L GPi	24.70	92.00	64.00	59.00	26.00	19.00	15.00	GD	Nocturnal dystonic spasms, SSI, Implant removal after 1.2 years
Case 2	GD-vascular insult (septum pellucidum AVM embolization)	9	10	11	2	Male	B/L GPi	31.93	59.50	44.50	29.50	11.00	8.00	6.00	GD: limbs>cranio-cervical	Nil
Case 3	Primary GD	0.75	11	12	11.25	Male	STN and GPi bilateral	21.73	72.00	60.00	58.50	24.00	28.00	20.00	GD: trunk>limbs, torticollis, dysarthria	Nil
Case 4	Dystonia-NBIA	7	10	12	5	Male	B/L GPi	16.80	88.00	64.00	70.00	25.00	20.00	23.00	GD with mental retardation, retinitis pigmentosa, ADHD	Nil
Case 5	Right hemi-dystonia	6	11	13	7	Male	Left STN+Left VOP	25.83	28.00	14.50	11.50	14.00	14.00	13.00	Right UL and LL Dystonia with dysarthria	Nil
Case 6	Wilson's disease	3.5	12	15	11.5	Male	B/L GPi	22.50	108.00	95.50	81.50	24.00	24.00	20.00	GD: limbs>cranio-cervical	Swallowing difficulty
Case 7	Wilson's disease	12	13	15	3	Male	B/L GPi	19.57	75.00	60.00	63.00	20.00	15.00	16.00	GD	Perioral movements
Case 8	DYT1-dystonia	9	11	16	7	Male	B/L GPi	13.10	64.00	23.00	16.50	9.00	3.00	3.00	GD: limbs>cranio-cervical, thoraco-lumbar kyphoscoliosis	Nil
Case 9	Primary GD	0.5	8	18	17.5	Female	B/L GPi	32.87	92.50	90.00	66.00	28.00	26.00	20.00	GD: limbs>cranio-cervical, limb contractures, torticollis	Nil
Case 10	DYT1+dystonia	8	8	11	3	Male	B/L GPi	12	85	1	1	22	1	1	GD	Nil

GD generalized dystonia, *NBIA* neurodegeneration with brain iron accumulation, *AVM* arterio-venous malformation, *B/L* bilateral, *GPi* globus pallidus internus, *STN* subthalamic nucleus, *VOP* ventralis oralis posterior, *UL* upper limb, *LL* lower limb

neuro-psychiatrists of the hospital. All the targets (GPi, STN, and VOP) were found suitable based on magnetic resonance imaging (MRI).

The mean age of onset, presentation, and surgery in our study population was 5.75 ± 3.91 years (range: 0.50–12 years), 10.05 ± 2.51 years (range: 4.50–13.0 years), and 13.11 ± 3.48 years (range: 6–18 years) respectively. The mean duration of disease before surgical intervention was 7.36 ± 5.21 years (range: 2.00–17.50 years). The mean follow-up duration was 23.22 ± 6.49 months (range: 13.10–32.87 months) (Table 2).

The mean pre-DBS motor score was 75.44 ± 23.53 which improved significantly at 6-month and 12-month follow-up to 57.27 ± 26.93 (p value 0.004) and 50.38 ± 24.90 (p value < 0.001). This improvement was found to be statistically significant after applying Bonferroni correction for multiple comparisons. While comparing sub-scores of BFMDRS, there was a significant difference in limb sub-scores. Pre-DBS limbs sub-scores were 48.11 ± 10.63 which improved to 36.11 ± 15.80 (p value 0.011) at 6 months and 32.22 ± 14.29 (0.002) at 12-month follow-up. This was a statistically significant improvement after the Bonferroni correction. Pre-DBS axial sub-score was 13.33 ± 5.29, at 6 months and 12 months it improved to 13.16 ± 6.21 (p value 1.00) and 10.44 ± 6.22 (p value 0.508), respectively. Similarly, pre-DBS face sub-score was 4.61 ± 4.54, at 6 months' 2.38 ± 2.47 (p value 0.119), and at 12 months 1.94 ± 2.80 (p value 0.188), pre-DBS speech and swallowing sub-score was 7.56 ± 5.34 which improved to 5.78 ± 5.65 (p value 0.425) at 6 months and remained the same (p value 0.425) at 12 months (Table 3; Fig. 2a).

The mean pre-DBS disability score was 20.11 ± 7.02 of the nine included patients in the study. It improved to 17.44 ± 8.30 at 6 months (p value 0.160) and 14.89 ± 6.64 at 12 months (p value 0.003) (Fig. 2b). Feeding (pre-DBS 2.56 ± 1.13 vs. at 6 months' 2.00 ± 1.58, p value 0.153 vs. at 12 months' 1.67 ± 1.32, p value 0.028), dressing (pre-DBS 3.11 ± 1.16 vs. at 6 months' 2.67 ± 1.41, p value 0.106 vs. at 12 months' 2.33 ± 1.11, p value 0.002), and walking (pre-DBS 4.56 ± 1.13 vs. at 6 months' 4.22 ± 1.48, p value 0.242 vs. at 12 months' 3.33 ± 1.00, p value 0.007) components of disability score improved significantly at 12-month follow-up post-DBS. However, speech (pre-DBS 2.67 ± 1.41 vs. at 6 months' 2.33 ± 1.11, p value 1.000 vs. at 12 months' 1.16 ± 1.11, p value 0.083), Writing (Pre-DBS 3.00 ± 1.22 vs. at 6 months' 2.56 ± 1.59, p value 0.106 vs. at 12 months' 2.56 ± 1.50, p value 0.106), eating and swallowing (pre-DBS 1.44 ± 1.66 vs. at 6 months' 1.22 ± 1.39, p value 1.000 vs. at 12 months' 0.89 ± 1.36, p value 0.153), and hygiene (pre-DBS 2.78 ± 1.09 vs. at 6 months' 2.44 ± 1.33, p value 0.242 vs. at 12 months' 2.33 ± 1.11, p value 0.106) sub-scores did not improve significantly at 6-month and 12-month follow-up (Table 3; Fig. 2c).

To estimate the effect of change of movement scores on the disability of the patients, correlation analysis was carried out. It showed a mean reduction of BFMDRS-M score at 6 months was 18.16 ± 11.23 (range: 2.50–41.00) and at 12 months was 24.83 ± 11.30 (range: 12.00–47.50). Similarly, the mean reduction of BFMDRS-D score at 6 months was 2.67 ± 3.53 (range: −4.00–7.00) and 5.22 ± 3.30 (range: 1.00–11.00). There was a positive correlation between the absolute reduction of the motor score and improvement

Table 3 Details of BFMDRS scoring of the study population

Motor score	Pre-DBS	6 months	12 months	Partial Eta squared*	P value* (6 months vs pre-DBS)	P value* (12 months vs pre-DBS)
Axis: neck and trunk (0–24)	13.33 ± 5.29	13.16 ± 6.21	10.44 ± 6.22	0.416	1.000	0.508
Limbs: lower and upper (0–64)	48.11 ± 10.63	36.11 ± 15.80	32.22 ± 14.29	0.791	0.011	0.002
Face: eyes and mouth (0–16)	4.61 ± 4.54	2.38 ± 2.47	1.94 ± 2.80	0.429	0.119	0.188
Speech and swallowing (0–16)	7.56 ± 5.34	5.78 ± 5.65	5.78 ± 5.65	0.250	0.425	0.425
Total	75.44 ± 23.53	57.27 ± 26.93	50.38 ± 24.90	0.764	0.004	< 0.001
Disability score						
Speech (0–4)	2.67 ± 1.41	2.33 ± 1.11	1.16 ± 1.11	0.475	1.000	0.083
Writing (0–4)	3.00 ± 1.22	2.56 ± 1.59	2.56 ± 1.50	0.508	0.106	0.106
Feeding (0–4)	2.56 ± 1.13	2.00 ± 1.58	1.67 ± 1.32	0.600	0.153	0.028
Eating and swallowing (0–4)	1.44 ± 1.66	1.22 ± 1.39	0.89 ± 1.36	0.423	1.000	0.153
Hygiene (0–4)	2.78 ± 1.09	2.44 ± 1.33	2.33 ± 1.32	0.500	0.242	0.106
Dressing (0–4)	3.11 ± 1.16	2.67 ± 1.41	2.33 ± 1.11	0.778	0.106	0.002
Walking (0–6)	4.56 ± 1.13	4.22 ± 1.48	3.33 ± 1.00	0.778	0.242	0.007
Total	20.11 ± 7.02	17.44 ± 8.30	14.89 ± 6.64	0.553	0.160	0.003

(*Repeated-measures ANOVA with Bonferroni correction)
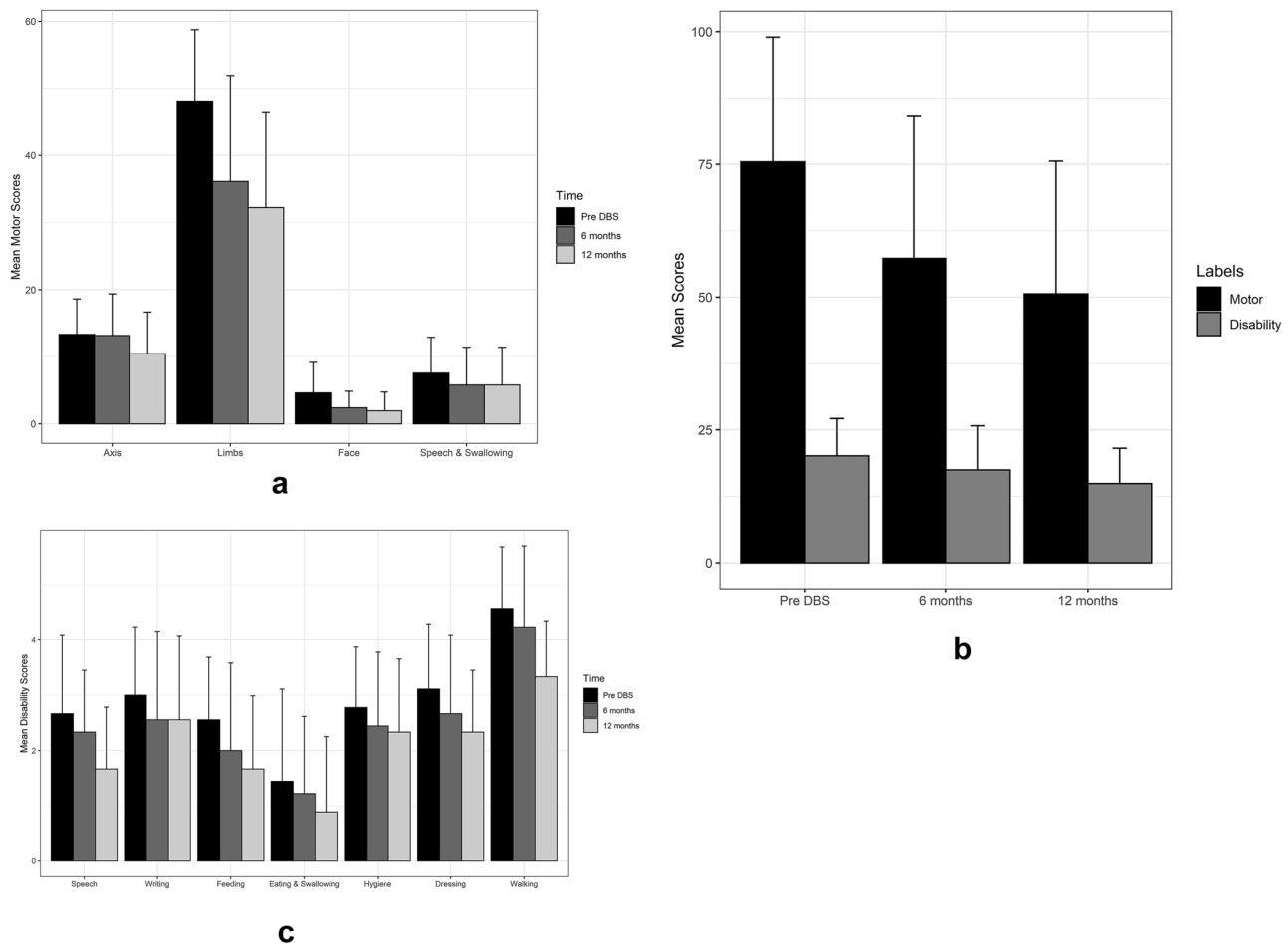
Fig. 2 Histograms showing **a** mean BFMDRS motor score changes, **b** mean BFMDRS combined score changes, and **c** mean BFMDRS disability score changes (pre-DBS and post-DBS at 6 and 12 months' follow-up)

in disability of the patients using Spearman's rank correlation at 6 months (rho = 0.865, p value 0.003). However, no correlation was found between them at 12 months of follow-up (rho = 0.527, p value 0.144) (Fig. 3a). There was 27.34 ± 18.78% (range: 2.70–64.06%) and 36.64 ± 20.36% (range: 16.00–74.21%) improvement in the BFMDRS-M score at 6 months and 12 months, respectively. Similarly, there was 17.37 ± 23.85% (range: − 16.67–66.67%) and 28.86 ± 19.47% (range: 7.14–66.67%) improvement in the BFMDRS-D score at 6 months and 12 months, respectively. There was no correlation found between the relative reduction of the motor score and relative improvement in disability of the patients using Spearman's rank correlation at 6-month (rho = 0.519, p value 0.152) and 12-month (rho = 0.400, p value 0.291) follow-up (Fig. 3b).

Discussion

Simplistically, dystonia encompasses a great number of genetic alterations under the broad term of primary dystonia and various identifiable structural pathologies under the category of secondary dystonia. *DYT-TOR1A (DYT1)* is the most common cause of hereditary dystonia which results from *TOR1A* gene-mutation [42]. As medical therapy bears unsatisfactory results, it forms a clear indication for DBS. Children with *TOR1A* deletion GPi DBS are found to be a beneficial target with reported improvement in BFMDRS-M ranging from 42.9 to 100% [17, 33, 42–44]. The only case in our study, #Case 8, showed 74.21% improvement following bilateral GPi DBS at 1-year follow-up with 67% improvement
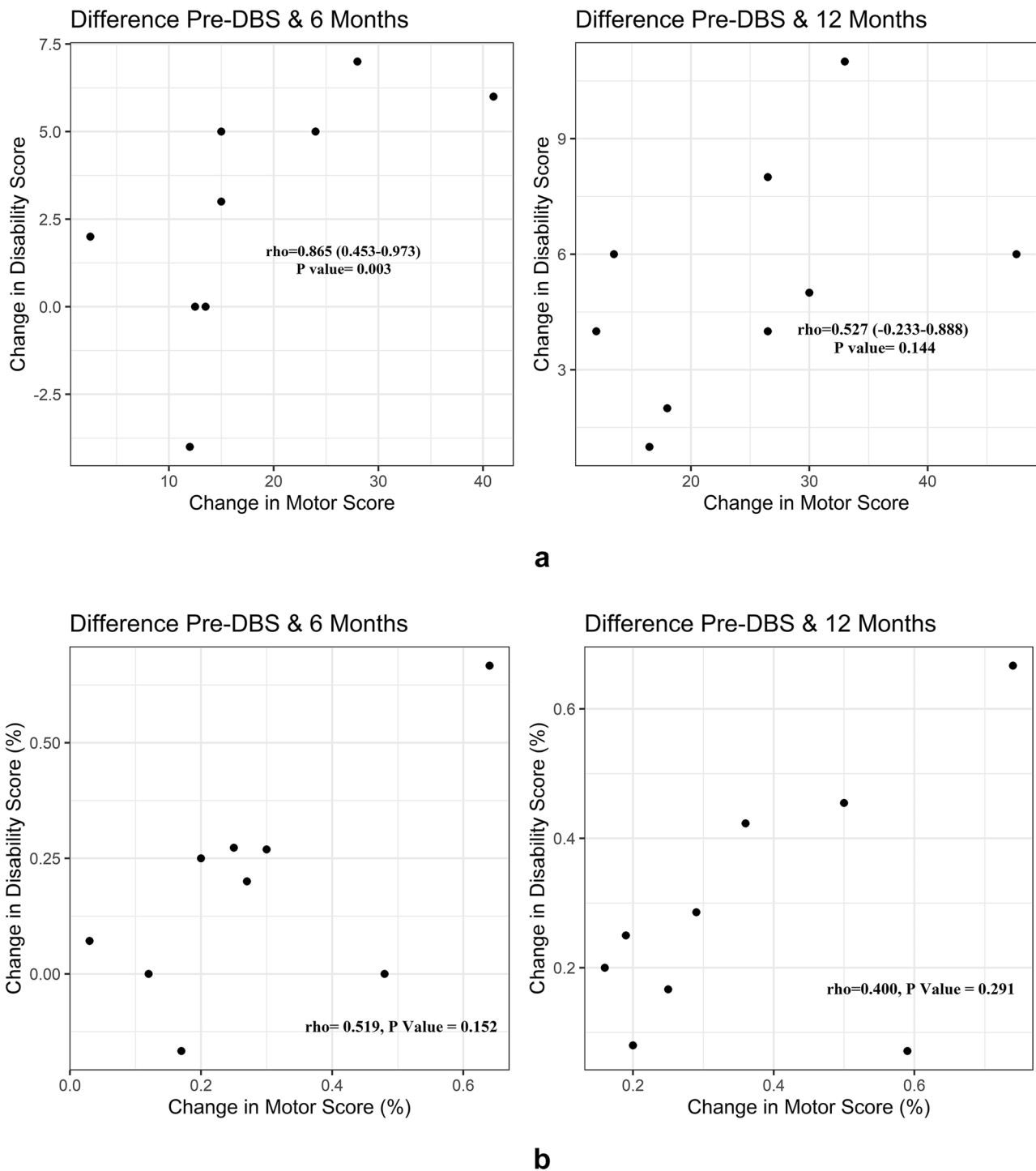
Fig. 3 Spearman correlation between **a** absolute changes and **b** relative changes of motor and disability sub-scores of BFMDRS at 6 and 12 months' follow-up

in disability (Table 2). This forms a strong argument for upfront genetic testing for all pediatric dystonia patients while selecting the optimum treatment strategy. One of the most common neurodegenerations with brain iron accumulation (NBIA) disorders is pantothenate kinase-associated

neurodegeneration (PKAN). DBS results in these cases are variable. A recently done meta-analysis showed a mean BFMDRS-M score improvement of 26% (range 15–37%) [45]. In our study, 2 cases were due to NBIA spectrum disorders (#Case 1 and #Case 4) which showed 35% and

20% improvement respectively in motor scores following bilateral GPi DBS. However, in published literature results of DBS with structural changes of basal ganglia, including Wilson's disease is variable. The average improvement reported in published literature is 25% on the dystonia rating scales. A case report, by Sidiropoulos et al., reported a 14% improvement in dystonia [46]. In our study, two cases (#Case 6, #Case 7) underwent bilateral GPi DBS. They showed 24% and 16% improvement respectively in BFMDRS motor scores.

Since the inception of surgical management of dystonia, various target sites have been explored which include globus pallidus internus (GPi), subthalamic nucleus (STN), dentate nucleus, and thalamus [47]. However, GPi has been the most explored and most effective target in pediatric dystonia [42]. But, due to the occurrence of stimulation-related bradykinesia, the requirement of high stimulation current causing reduced battery life, new stimulation-induced gait, and fine motor complications, various other targets are also being explored [48–50]. In a recent study, Ostrem et al. reported an improvement in BFMDRS motor scores by 70.4% at 3 years to follow-up with a significant improvement in disability and quality of life parameters [51]. Various studies compared the efficacy of GPi and STN DBS and concluded both to be equally effective in treating the same. In their study, Schjerling et al. found that BFMDRS movement scores improved by 13.8 and 9.1 points after STN and GPi stimulation, respectively [52]. Lin et al. in their study found that STN (64%) and GPi DBS (48%) cause 64% and 48% improvement in BFMDRS motor score at 12-month follow-up [53]. However, in a recent meta-analysis, there was no significant difference between STN and GPi DBS [47]. GPi is recommended to be a good target for primary generalized and segmental dystonia (Level A Evidence) and cervical dystonia (Level B) by the European Federation of the Neurological Societies (EFNS) [4]. However, GPi DBS is less effective for secondary dystonia (Level C) [4]. In our study, the majority of the patients underwent B/L GPi DBS. Only two patients underwent STN and VOP DBS (#Case 3 B/L STN and GPI, Case5 Left STN and VOP). The selection of the most appropriate target is still heavily debated [47].

In the descriptive literature, younger age at surgery (< 21 years), shorter duration of symptoms before surgery (< 15 years), and DYT1-positive status were found to be associated with better prognosis [6]. In our study, the mean duration of disease before surgical intervention was 7.36 ± 5.21 years. All the patients barring one patient (#Case 9) had a duration of disease less than 15 years. The mean improvement in motor score was $27.34 \pm 18.78\%$ in our study, and this case (#Case 9) had a 28.64% improvement. As postulated previously, the different levels of

cortical plasticity and endophenotype might account for this differential effect [54].

In our study, we have found that patients with both primary and secondary dystonia improve significantly following DBS. If we take a 20% improvement in BFMDRS motor score as the cut-off for meaningful clinical improvement, seven out of nine patients (77.78%) attended this endpoint at 1-year follow-up which is significantly better than the reported levels (66%) in a recent meta-analysis [55]. All our patients showed improvement in motor sub-scores in BFMDRS score which was higher than the reported 86% cases in their study [55].

A recent systematic review concludes that individuals diagnosed with primary dystonia exhibited a higher likelihood of experiencing a notable enhancement of $\geq 50\%$ in BFMDRS-M scores, reaching 56%, in contrast to patients with secondary forms of dystonia, among whom only 21% achieved similar improvement (*p* value 0.004) [56]. Within the DYT1 + subgroup, there was a greater propensity for a $\geq 50\%$ enhancement in BFMDRS-D, with a rate of 65%, in comparison to DTY1 − individuals, among whom this improvement was observed in only 29% (*p* value 0.02) [56]. Notably, there were no discernible disparities in the rates of $\geq 50\%$ improvement in BFMDRS-M scores between DYT1 + (66%) and DYT1 − (43%) children (*p* value 0.11) [56]. Different studies in the published literature indicate diverse levels of motor improvement in secondary dystonia and NBIA following DBS with a mean of $18.12\% \pm 29.44\%$ (range: − 63.33% to 72%) (Table 4) [19, 22, 25, 33, 37]. The average duration of symptoms in cases of secondary dystonia and NBIA (#Cases 1, 2, 4, 6, 7) in our study is 4.7 years (range: 2–11.5 years), compared to 8.6 years (range 4–13.7 years) in the published literature (Table 4). The mean improvement in motor score for secondary dystonia in our study is $29.46 \pm 13.85\%$ (range: 16–50.42%) (Table 2). Therefore, the improved motor outcomes for this patient group in our study could be attributed to the early surgical intervention in these cases.

While we did the motor sub-score analysis, there was a significant improvement in limb sub-scores following DBS at 6 months and 12-month follow-up. On the BFMDRS disability scale, there was significant improvement at 1 year but not at 6 months. This means although the motor score improves significantly at 6 months, it takes additional time for this effect to translate into improvement of disability. There was a positive correlation between improvement in movement subscore and reduction in disability at 6 months. Under the disability sub-scores, feeding, dressing, and walking components improved significantly at the end of 1 year, which should indirectly reduce the burden on caregivers from constantly taking care of these patients.

Table 4 A pooled analysis of the outcomes of studies in the published literature on children with secondary dystonia and NBIA undergoing DBS

Author	Age at onset of symptoms (years)	Age at surgery (years)	Duration of symptoms (years)	Sex	Genetic status	Type of dystonia	Pre-op BFMDRS-M score (motor score)	Post-op BFMDRS-M score (motor score)	Change in BFMDRS-M (%)
Ghosh et al. (2012) [22]	5	13	8	NR	NA	SGD (mitochondrial disorder)	NR	NR	-
	13	21	8	NR	NA	SHD (TBI)	NR	NR	-
Keen et al. (2014) [25]	0	8	8	F	NA	Dystonic CP (HB)	68.5	36	47.44
	0	17	17	M	NA	Dystonic CP (HIE)	97.5	71	27.17
	10	14	4	M	NA	Dystonic CP (meningitis)	60	41	31.66
	0	7	7	M	NA	Dystonic CP (HIE)	102	80	21.56
	7	11	4	M	NA	Intracerebral hemorrhage	38.5	34	11.68
	6	13	7	M	Not collected	HS	92	36	60.86
Olaya et al. (2013) [19]	NR	20	NR	M	Unknown	Axonal brain injury	82	57.5	29.87
	NR	16	NR	M	Unknown	CP	90.5	90.5	0
	NR	20	NR	M	Unknown	CP	90	53.5	40.55
	NR	10	NR	M	Unknown	Kernicterus	94.5	94.5	0
	NR	20	NR	F	Unknown	CP	108	108	0
	NR	20	NR	M	Unknown	CP	58	53.5	7.75
	NR	19	NR	F	Unknown	CP	106	100	5.66
	NR	6	NR	M	Unknown	CP	76	76	0
	NR	16	NR	M	Unknown	Kernicterus	73	NR	
Petrossian et al. [33]	9	17	8	M	PANK2+	SGD	86	75	12.79
	9	15	6	M	PANK2+	SGD	30	49	−63.33
	NR	17	NR	NR	Unknown	CP	82	51	37.80
Zorzi et al. [37]	1.5	14	12.5	M	Unknown	Basal ganglia calcifications	59	16	72.88
	0.5	14.2	13.7	M	Unknown	Encephalopathy of unknown origin	43	43	0
Mean (range)			8.6 (4–13.7)						18.12 ± 29.44% (−63.33–72%)

All adverse effects are usually challenging in pediatric dystonia as it necessitates hospital admission which hampers patients' quality of life significantly. In our series, three patients had adverse events, in the form of stimulation-induced adverse effects (new-onset nocturnal dystonic spasms, swallowing difficulty, and perioral movement) and wound infection. In a German registry–based study, stimulation-induced adverse effects were observed in 23.6% of cases and wound infections were documented in 12.5% of cases [57]. The overall complication rate is relatively higher in very young children. All these factors including

therapeutic misadventures should be taken into account while counseling the patients and treating teams should follow standardized management algorithms to achieve desired clinical goals [57].

In light of the current evidence, it might be tempting to believe that DBS is the panacea in the treatment of dystonia which will be a gross exaggeration of facts. In carefully selected patients with dystonia, the degree of improvement ranges from 21 to 95% [58]. Distortion in anatomical targets in secondary dystonia makes it remarkably difficult to properly identify the targets. Even after successful stimulation

with clinically meaningful recovery, patients often need adjunctive treatments in the form of medications and botulinum toxin injections. The therapeutic goals in these cases are directed toward ameliorating involuntary movements, correcting abnormal postures, reducing pain, preventing contractures, and improving the overall quality of life. So multidisciplinary teamwork is mandatory to achieve sustainable clinical benefits. Active participation of all stakeholders including the treating team, patients, and caregivers with therapeutic realism instead of nihilism is imperative to achieve these goals.

The strengths of our study lie in the fact that our reported series of 10 cases in pediatric dystonia is the second largest (largest being Petrossian et al. [33] of 13 cases) in the world literature and the majority of the reported cases in those series are *DYT1+* which is known to have excellent outcome following DBS. In many of those series, the upper age limit for the surgery has been kept at 21 years as compared to 18 years in our series. Despite having a lower cut-off for age and only one patient being DYT1+, our series is not only more voluminous than the most but our results are also comparable to those in the published literature. Although it is a retrospective study by definition, because of the well-established strict follow-up protocols of the hospital, the follow-up assessments were done at strict intervals of 6 and 12 months. The statistical analysis was robust examining interplays between multiple factors to reach a meaningful conclusion which is supported by published literature worldwide. Uniformity of the study was ensured as all the cases were operated by a single senior neurosurgeon (DS) and were under the treatment of a dedicated movement disorder team.

Conclusion

This is the second-largest study reported in the world on pediatric dystonia from a high-volume tertiary care center with a dedicated movement disorder team. DBS in carefully selected cases of pediatric dystonia has a significant role in reducing disease burden and a sustainable therapeutic goal is achievable in most cases when performed by a dedicated team with the required expertise. Based on the findings of this study, future double-blinded prospective studies can be designed to make a predictive model for better and broader patient selection and to explore and identify various alternative targets.

Declarations

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