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Original article

Gross motor function outcomes following deep brain stimulation for childhood-onset dystonia: A descriptive report

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ABSTRACT

Aim: To examine the impact of deep brain stimulation (DBS) on gross motor function in children with dystonic movement disorders.
Method: Prospective audit involving children implanted 2007–2015, followed for up to two years. Outcomes were evaluated across aetiological sub-groups (inherited, acquired, idiopathic) using the GMFM-88 and BFMDRS movement scale (BFM-M). The predictive value of proportion of life lived with dystonia (PLD) and baseline motor capacity were evaluated.
Results: Data was available for 60 children (median surgery age 10y11mo). Inherited monogenetic dystonias demonstrated a median increase in GMFM-88 scores of 6.9% ($p = 0.021$) and 14.5% ($p = 0.116$) at one and two years. Heredodegenerative and idiopathic dystonias showed disparate responses, with non-significant changes seen in GMFM-88 and BFM-M scores, with the exception of improved one-year BFM-M scores in the idiopathic group [median change 5.5, $p = 0.021$]. Median GMFM-88 and BFM-M change scores were near zero for acquired dystonias, though improvement was noted in 9/18 CP cases with one-year GMFM-88 data. No significant relationship was found between PLD, or baseline GMFM-88, and GMFM-88 change following DBS.
Conclusion: Gross motor response to DBS is similar in profile to literature reporting results using impairment-based dystonia rating scales. Relatively consistent improvements were seen in inherited monogenetic ("primary") dystonias, while highly variable, often disappointing, gross motor responses were found in acquired, heredodegenerative, and idiopathic dystonias. In view of such response variability, alternatives to mean group studies, such as single case experimental designs with multiple replications, are needed to determine the efficacy of DBS in childhood-onset dystonias. Ongoing research is needed to identify factors that predict treatment response.

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1. Introduction

Dystonia aetiologies are diverse,[1] varying from intermittent and focal involuntary muscle contractions to generalised dystonia with widespread involvement of axial and limb musculature. In contrast to adults, where focal primary dystonias are more prevalent, secondary dystonic disorders predominate in the paediatric population,[2] while primary dystonias of childhood tend to generalise in the first decade of life.[3] A recent review of children referred for specialist dystonia management suggests dystonia worsens over time in the majority of cases, with a minority remaining static or improving spontaneously, irrespective of aetiology.[4] This aligns with reports that dystonia in children frequently proves refractory to medical management, with adverse effects often limiting effective symptom control.[5] Such issues have raised considerable interest in deep brain stimulation (DBS) as a therapeutic option for the management of paediatric dystonia.[6,7]

Although the precise mechanism of action has yet to be definitively elucidated, DBS may directly reduce pain and immobility associated with dystonia, thereby improving functional ability and indirectly reducing carer burden.[8] A review of DBS in predominantly adult patients concluded that pallidal DBS offered reliable dystonia improvement and acceptable safety when applied to primary dystonias, myoclonus-dystonia and tardive dyskinesias, with inconsistent, and at times disappointing, outcomes in secondary dystonias.[9] Precise prediction of DBS outcome for the individual patient remains an elusive goal, particularly in secondary dystonias.[9–11] It has been suggested a lower proportion of life lived with dystonia,[12] or intervention prior to skeletal maturity,[13] may correlate with greater reduction in dystonia following DBS, while non-invasive neurophysiology testing may offer prognostic value.[14] There are even fewer data regarding the magnitude and time course of functional recovery or acquisition of motor skills following DBS in paediatric movement disorders and, despite specific recommendations,[15] reports of gross motor function outcomes in this population are lacking.

Gross motor function involves the use of large groups of muscles to maintain balance and change positions (e.g. sitting, crawling, walking, running and jumping), abilities typically well established by age 5 years. Along with intellectual disability,[16] gross motor function has been identified as an important predictor of everyday activities in mobility, self-care and social function.[17] Children and parents contemplating DBS surgery frequently identify recovery or improvement of gross motor function and everyday activities as primary goals,[18] though there is little published literature to guide clinicians and families in the attainability of such goal areas.

This prospective clinical audit reports gross motor function following DBS in 60 children with dystonic movement disorders, systematically followed for up to two years using the Gross Motor Function Measure (GMFM-88).[19] We hypothesised that DBS would improve gross motor function and anticipated greater improvements in children with primary inherited and idiopathic dystonias, compared to secondary/acquired and heredodegenerative forms. We also wished to explore the prognostic value of baseline gross motor function and proportion of life lived with dystonia (PLD) on gross motor outcomes following DBS.

2. Method

2.1. Participants

A total of 131 successive children were formally evaluated by a physiotherapist prior to DBS surgery at our institution between 2007 and 2015. Patients were included in the study provided a minimum of one-year post-operative GMFM-88 data was available, irrespective of whether patient specific DBS goals included improving gross motor function. Results are presented for the first two years of patient follow-up.

All cases presented with disabling dystonia, refractory to conventional medical management, and judged to have little or no significant spasticity or corticospinal tract impairment based on clinical assessment, neuroimaging, and central motor conduction time.[20] Cases were excluded from the study on the basis of explantation or device malfunction occurring within the first year of follow up. Malfunction was defined as i) DBS switched off at the time of formal review; ii) frequent or prolonged switching off during follow up; iii) high impedances on greater than one contact.

2.2. Procedure

DBS surgery and pulse generator programming were performed as previously described,[12] with bilateral posteroventrolateral globus pallidus internus (GPi) targeted in all cases. Post-operative in-frame stereotactic computerised tomography imaging confirmed DBS electrode position in the target GPi.[21] All children underwent routine pre-operative clinical evaluation, including characterisation of movement disorder phenotype, screening for significant deformity, and pre- and post-operative motor and function assessments. Assessments took place no more than four months prior to surgery and yearly post-operatively. Therapists were not blinded to treatment status. As the audit involved data collected as part of routine clinical practice and anonymised prior to data analysis, ethics approval was not required and consent was neither required nor obtained from participants.

2.3. Aetiology and severity classification

In line with other groups,[22] patients were pragmatically categorised according to the new international classification,[23] effectively generating four aetiological groups: inherited dystonia (group 1a isolated monogenetic dystonia, group 1b heredodegenerative dystonia), group 2 acquired dystonia, and group 3 idiopathic dystonia. The classification of Geyer and Bressman (2006)[24] was used to separate so-called "secondary dystonias" into hereditary and acquired forms.

Pre-operative functional mobility status was described using the Gross Motor Function Classification System (GMFCS),[25] assigning a "GMFCS equivalent" score to non-cerebral palsy (CP) cases.[26] The proportion of life lived with dystonia (PLD) was

defined as the duration of dystonia divided by age at DBS surgery. Onset of dystonia was determined through review of the clinical record, with additional parental consultation when age of onset was not clear in the medical notes.

2.4. Outcome measures

Service physiotherapists formally evaluated gross motor function using the GMFM-88.[19] In order to minimise variability related to external factors, subjects were tested without shoes (exception: stair items), orthotics or mobility aids, and using standardised equipment. In five cases (aetiological groups 1a n = 3, group 3 n = 2) with high baseline functional abilities, lying, sitting ± crawling/standing test dimensions were omitted at some time points in the interest of time and improved test sensitivity. In these cases, averaged dimension scores were consistently substituted for total scores at all time points (see Table S1, supplementary online information).

Dystonia was evaluated using the Burke-Fahn-Marsden dystonia rating movement scale (BFM-M),[27] with test administration as previously outlined.[28] Although originally established for the quantitative assessment of primary torsion dystonias in adults, the BFM-M has been widely used in other forms of dystonia including CP.[11,13,29] The BFM-M scores of some cases included in this manuscript have been previously reported.[12,28]

2.5. Statistical methods

Statistical analyses were performed using the Statistical Package for Social Sciences, version 23 for Windows (SPSS Inc., Chicago, IL, USA) and the R language and environment for statistical computing, version 3.0.1 64-bit for Windows. Non-parametric approaches were used where data were not normally distributed. Differences between aetiological subgroups were assessed using the Kruskal-Wallis test (KW). Differences between baseline and follow-up scores were examined using the Wilcoxon Signed Rank test (WSR). Relationships between continuous or ordinal variables were evaluated using Pearson correlation (r) when a roughly linear relationship was found and Spearman correlation (r_s) otherwise. In all cases a p-value<0.05 was considered statistically significant. The impact of individual observations was evaluated using Cook-type distances, while potential confounders were assessed using multivariate linear models. Where repeated measurements were assessed, graphical checks for regression to the mean were carried out[30] to determine the need for Oldham's transformation.[31] Where none was found, simple Spearman correlations were retained.

3. Results

3.1. Descriptive results

Sixty patients met inclusion criteria: 28 female, 32 male. Twenty-five were classified into group 1 inherited dystonias (group 1a n = 11, group 1b n = 14), 20 were acquired disorders (group 2), and 15 idiopathic (group 3). The aetiological cause of dystonia was very heterogeneous (see supplementary online Table S1), the cohort including group 1a n = 5 DYT1 cases, group 1b n = 4 pantothenate kinase associated neurodegeneration (PKAN), n = 2 Lesch-Nyhan, n = 2 glutaric aciduria type 1 (GA1), n = 3 mitochondrial disorders; group 2 n = 19 CP (n = 7 hypoxic ischaemic encephalopathy (HIE), n = 3 kernicterus, n = 9 preterm delivery). One year GMFM-88 data were available for 57 individuals, two-year data for 41 cases. BFM-M data were available for all subjects at one year, and for 44 patients at two years. Six cases were excluded from the study on the basis of explantation or device malfunction occurring within the first year of follow up. Two were excluded due to rater errors in scoring. Patient inclusion and missing data are presented in Appendix 1, while individual patient characteristics and results are shown in Table SI, both provided as supplementary online information. Group demographics and group results are summarised in Table 1.

The median age at surgery was 11 years 1 month (IQR 7 years 4 months–14 years 8 months). Although mobility status was distributed across GMFCS levels (levels: I [n = 4], II [n = 9], III [n = 8], IV [n = 23], V [n = 16]), two-thirds of cases (39/60) were non-ambulant at pre-operative assessment. The median preoperative GMFM-88 score for the entire cohort was 41.8 (IQR 18.3–79.8), while the median BFM-M was 77.5 (IQR 58.4–88.9). Age at surgery was not statistically different between aetiological groups (p = 0.521), though there were significant differences in age of onset of the movement disorder (p < 0.001) and PLD (p < 0.001). Post hoc analysis via pairwise comparisons revealed earlier age of onset and longer PLD in acquired (group 2) dystonias when compared with other groups (KW group 2 vs 1a p < 0.001; vs 1b p = 0.001; vs 3 p < 0.001).

The distributions of baseline GMFM-88 and BFM-M scores were also significantly different between aetiological groups (p = 0.005 and p = 0.001 respectively). Post hoc pairwise comparisons showed better baseline gross motor function and less severe dystonia in group 1a inherited dystonias (GMFM-88 mean rank 43.0, BFM 14.5) than both acquired (group 2 GMFM-88 mean rank 23.7, p = 0.019, BFM 36.7, p = 0.004) and heredodegenerative groups (group 1b GMFM-88 mean rank 23.8, p = 0.038, BFM 38.8, p = 0.003). These differences persisted at all time points.

3.2. Differences between baseline and post DBS implantation

The overall median GMFM-88 score increased from 41.8 to 59.7 (IQR 23.9–91.6) at one year, a difference that was found to be significant (p = 0.002). Of the 57 cases with one year GMFM-88 data, 40 exhibited positive score change and 17 decline. A fall-off was seen in GMFM-88 scores at two years (median 45.6, IQR 23.7–79.3), with differences no longer statistically significant (p = 0.683). A similar pattern was noted in BFM-M scores, with improvements significant at one year (median 72.5, IQR 49.1–88.5, p = 0.006), but not at two years (77.5, IQR 58.3–91.3, p = 0.262).

Group 1a inherited dystonias demonstrated a median improvement in GMFM-88 total scores of 6.4% (IQR 0.7–37.7) at one year and 14.5% (IQR -1.5 – 31.9) at two years (Fig. 1), though these differences reached statistical significance at one year only (p = 0.016; 2 year p = 0.116). Improvements were

Table 1 – Baseline characteristics and GMFM-88 and BFM-M scores for each aetiological sub-group.

Demographic details	Whole group	Group 1a	Group 1b	Group 2	Group 3
		Inherited monogenetic dystonias	Heredo-degenerative dystonias	Acquired dystonias	Idiopathic dystonias
Group size	n = 60	n = 11	n = 14	n = 20	n = 15
Males/females	32/28	2/9	9/5	11/9	10/5
Age at surgery y:mo (range)	11y1mo (7y4mo – 14y8mo)	11y10mo (7y4mo – 18y9mo)	11y1mo (4y2mo – 17y5mo)	10y8mo (5y4mo – 17y10m)	12y2mo (6y9mo – 18y7mo)
PLD (range)	0.85 (0.54–0.96)	0.57 (0.11–0.97)	0.82 (0.07–0.95)	0.97 (0.14–1.0)	0.82 (0.25–0.98)
GMFCS I-III/IV-V	21/39	8/3	1/13	3/17	9/6
Baseline GMFM-88	41.8 (18.3–79.8)	78.4 (31.9–99.3)	29.1 (15.2–52.7)	31.3 (15.9–48.9)	85.8 (16.8–92.7)
One year GMFM-88	59.7 (23.9–91.6)	94.4 (81.4–99.4)	38.2 (26.3–57.7)	34.6 (18-8 – 59.1)	81.3 (36.1–94.0)
n	n = 57	n = 11	n = 13	n = 19	n = 14
Absolute change	1.7 (−1.0 – 8.4)	6.4 (0.7–37.7)	0.8 (−2.9 – 7.8)	0.9 (−2.5 – 5.6)	2.2 (−0.9 – 9.7)
WSR test	***p = 0.002****	***p = 0.016****	*p = 0.422*	*p = 0.178*	*p = 0.056*
Two year GMFM-88	45.6 (23.7–79.3)	*98.6 (71.4–99.7)*	28.8 (18.3–54.1)	41.5 (15.3–50.4)	71.3 (39.7–91.0)
n	n = 41	*n = 6*	n = 12	n = 13	n = 10
Absolute change	0.12 (−4.1 – 9.4)	*14.5 (1.5–31.9)*	−2.0 (−15.6 to −0.7)	0.1 (−4.2 - 3.6)	5.2 (−3.1 – 19.2)
WSR test	*p = 0.683*	*p = 0.116*	*p = 0.060*	p = 0.861	*p = 0.169*
Baseline BFM-M	77.5 (58.4–88.9)	57 (50.0–70.0)	85 (77.3–90.0)	83.3 (74.0–85.0)	60 (58–98)
One year BFM-M	72.0 (49.1–88.5)	16.0 (10.0–64.0)	93.5 (68.8–97.0)	77.8 (72.0–84.5)	57.5 (40.5–74.5)
n	n = 60	n = 11	n = 14	n = 20	n = 15
Absolute change	2.5 (−2.9 – 13.8)	15.0 (2.5–37.0)	−2.0 (−12.3 – 6.0)	0.8 (−3.0 – 6.8)	5.5 (−1.5 - 19.5)
WSR test	***p = 0.006****	***p = 0.003****	*p = 0.510*	*p = 0.456*	***p = 0.021****
Two year BFM-M	77.5 (58.3–91.3)	22.5 (16.3–53.5)	89.0 (73.0–99.5)	83.3 (73.0–92.0)	64.5 (46.0–74.5)
n	n = 44	n = 7	n = 13	n = 14	n = 10
Absolute change	1.3 (−6.6 – 12.5)	13.0 (5.0–47.0)	−4.0 (−15.0 – 6.3)	−3.0 (−5.9 – 3.0)	9.0 (−4.8 - 32.6)
WSR test	*p = 0.262*	***p = 0.028****	*p = 0.463*	*p = 0.286*	*p = 0.103*

Baseline characteristics presented as median (min–max). Absolute scores and change scores given as median (25th to 75th centile). Statistically significant changes marked by an asterisk p < 0.05. BFM-M = Burke-Fahn–Marsden Dystonia Rating Movement Scale; DBS, deep brain stimulation; F, female; GMFCS = Gross Motor Function Classification Scale or equivalent; GMFM-88 = Gross Motor Function Measure 88-item scale; M, male; PLD = proportion of life lived with dystonia; WSR = Wilcoxon rank sum test.
Bold italics text represents clinically significant results (p < 0.05).

consistently seen in the BFM-M (Fig. 2), with a median reduction of 15.0 points (IQR 2.5 to 37.0, p = 0.003) at one year and 13.0 points (IQR 5.0 to 47.0, p = 0.028) at two years.

As highlighted in Fig. 1, heredodegenerative dystonias (group 1b) showed very disparate responses, some cases improving, at least temporarily, others notably declining over time. The net result was that group change over time did not reach statistical significance, with median GMFM-88 change scores of 0.8 at one year (IQR -2.9 to 7.8; p = 0.422) and −2.0 at two years (IQR -15.6 to −0.7; p = 0.060). Similarly disparate responses were seen in BFM-M scores (Fig. 2), with no significant difference in follow up scores (one year median change −2.0, IQR -12.3 to 6.0; p = 0.510; two years median change −4.0, IQR -15.0 to 6.3; p = 0.463).

Although improvement in GMFM-88 scores were seen in some individuals with acquired dystonias (group 2. Fig. 1), at a group level median change scores were near zero and differences failed to reach statistical significance at either time point (one year median change 0.9, IQR -2.5 to 5.6, p = 0.178; two years median change 0.1, IQR -4.2 to 3.6, p = 0.861). BFM-M group scores (Fig. 2) also failed to show significant differences following DBS (one year median change 0.8, IQR -3.0 to 6.8; z = −0.745, p = 0.456; two years median change −3.0, IQR −5.9 to 3.0; p = 0.286).

Response in the group 3 idiopathic cases varied considerably (Fig. 1), some cases showing obvious improvement in motor function, others notable decline. Differences in GMFM-88 scores were not statistically significant at either time point (one year median change 2.2, IQR -0.9 to 9.7, z = 1.915, p = 056; two years median change 5.2, IQR -3.1 to 19.2, z = 1.376, p = 0.169). By contrast, dystonia scores improved at one year (median BFM-M change 5.5, IQR -1.5 to 19.5, z = −2.302, p = 0.021, Fig. 2), with a similar trend to improvement at two years that did not reach statistical significance (median 9.0, IQR -4.8 to 32.6, z = −1.632, p = 0.103).

Post hoc analysis confirmed these general trends were also consistent across the five GMFM subtest dimensions A-E (see supplementary online Figures S1 To S5). We note that, for group 1a dystonias, the degree of change in dimensions C and E seems bigger than in other dimensions, and for other subtypes. The differing amount of change between dimensions likely relates to thresholding (where scores are close to minimum or, in this case, maximum test values), limiting the potential for change.

3.3. *Association between dystonia and gross motor function*

More severe dystonia was associated with greater motor disability, as demonstrated by a strong inverse association between BFM-M & GMFM-88 total scores at all time points (baseline $r_s = -0.811$ [see Fig. 3], 1 year $r_s = -0.839$, 2 years $r_s = -0.795$; all $p < 0.001$). A positive relationship was seen between change in BFM-M and change in GMFM-88 at both

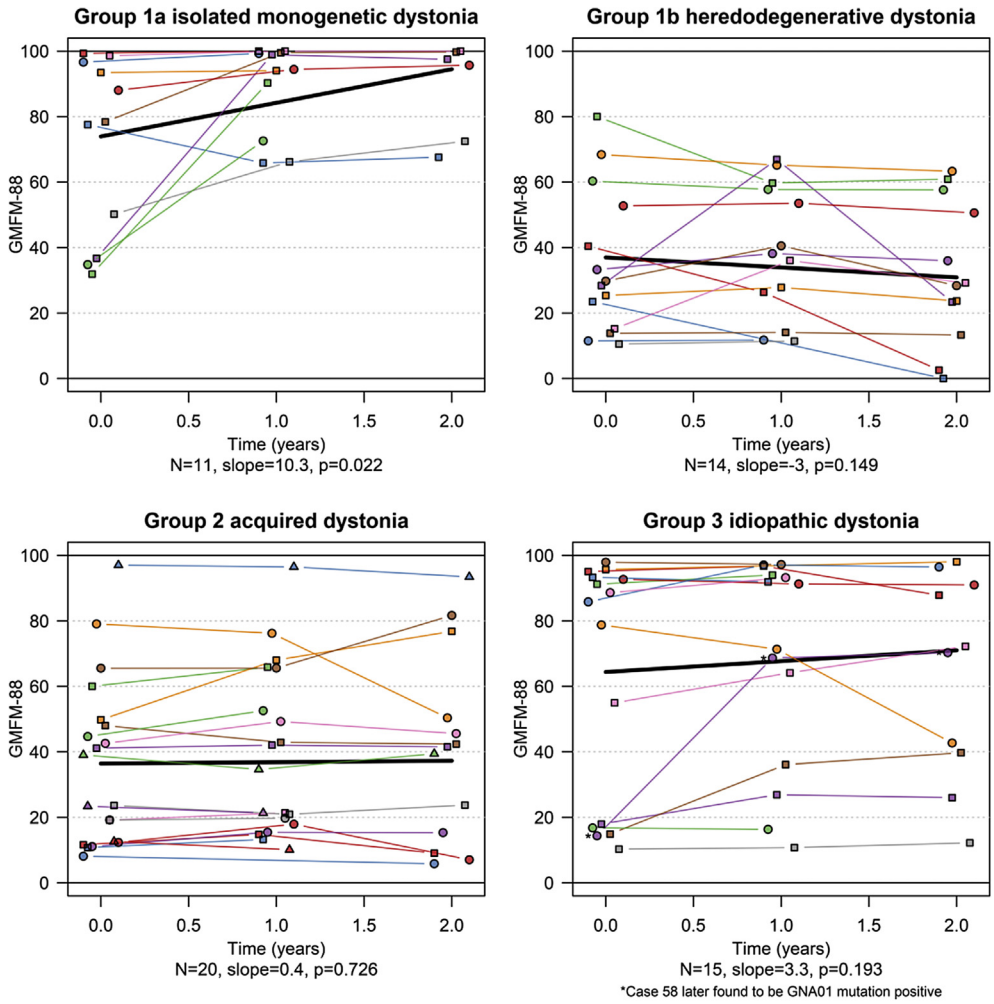

Fig. 1 – Individual patient change in GMFM-88 scores at 1 and 2 years post DBS, according to aetiological subgroups.

one and two years ($r_s = 0.388$, $p = 0.003$ and $r_s = 0.552$, $p < 0.001$ respectively), reflecting a trend for improved gross motor function with reduction in dystonia.

3.4. *Predictive factors: proportion of life lived with dystonia (PLD) and baseline motor function*

No significant relationship was found between either of the variables, PLD or baseline GMFM-88, and GMFM-88 change following DBS [PLD 1 year r_s = -0.154, p = 0.253; 2 years rs = -0.079, p = 0.624; baseline GMFM88 1 year r_s = -0.202, p = 0.133; 2 years r_s = -0.155, p = 0.332].

4. Discussion

Current knowledge regarding functional outcomes following DBS in children is limited. The available literature describes favourable responses in primary dystonias, with more modest and highly variable responses in dystonias acquired as a result of exogenous injury or neurodegenerative disease processes. However, outcomes are typically reported utilising dystonia scales that evaluate the impairment domain of the World Health Organisation's International Classification of Functioning, Disability and Health (ICF),[32] and, with the exception of a single case study,[33] we are not aware of published reports of gross motor function outcomes following paediatric DBS.

This paper explores the effect of DBS on gross motor function in childhood-onset dystonias using the GMFM-88. As hypothesised, the majority of children with inherited monogenetic (previously categorised as "primary/primary-plus") movement disorders demonstrated gross motor improvement following DBS, with gains consistently seen in DYT1 positive subjects. Only one case, with LMNA gene mutation associated with progressive neuromuscular weakness followed by onset of a movement disorder in later childhood, exhibited decline in gross motor skills following DBS. This decline appeared related to progression in underlying muscle weakness, with subjective stable improvement in dystonia and chorea. Of two cases with KMT2B mutations, one demonstrated appreciable gains in gross motor skills and functional mobility that was sustained over the two year follow up, despite little change in the BFM-M score. In the other case, the initial post-operative course was complicated by gait freezing and worsening axial dystonia, responsive to DBS changes. Gross motor skills subsequently stabilised, though longer-term effects are unclear due to device malfunction in the second year. The presence

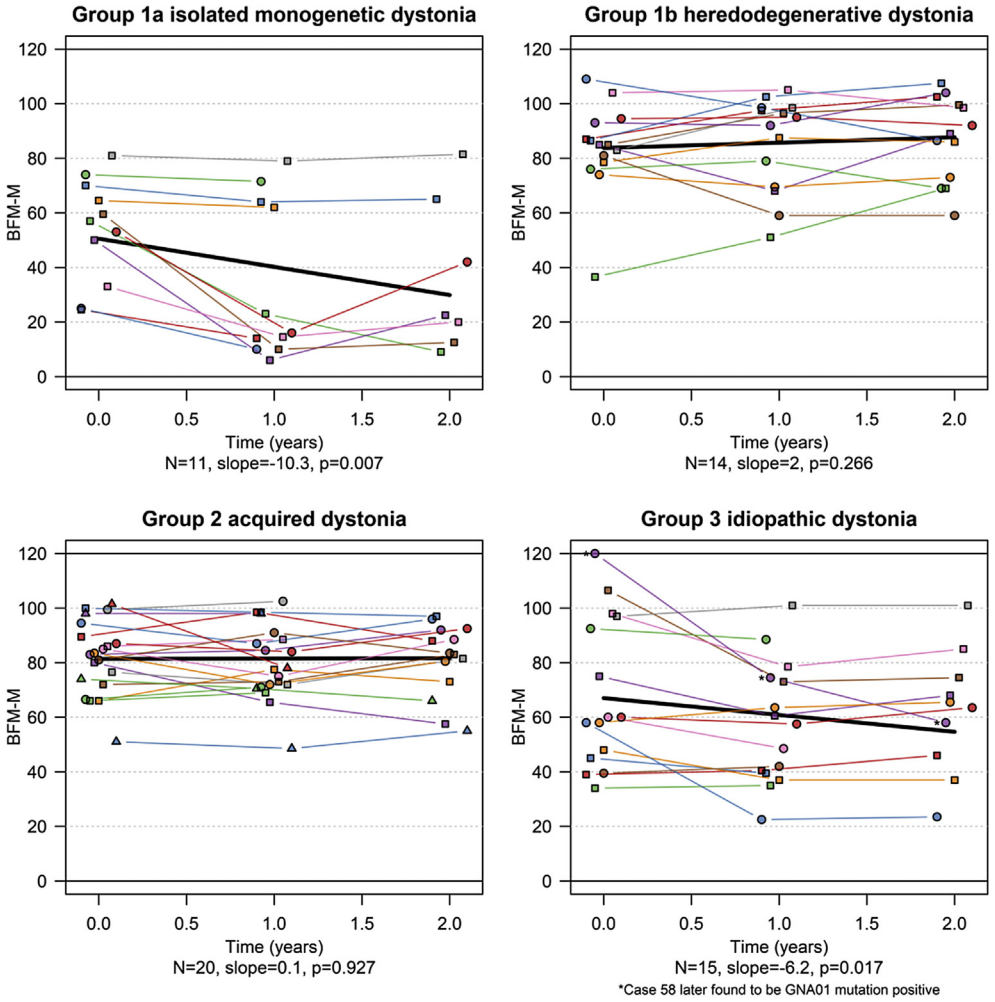

Fig. 2 – Individual patient change in BFM-M at 1 and 2 years post DBS, according to aetiological subgroups.

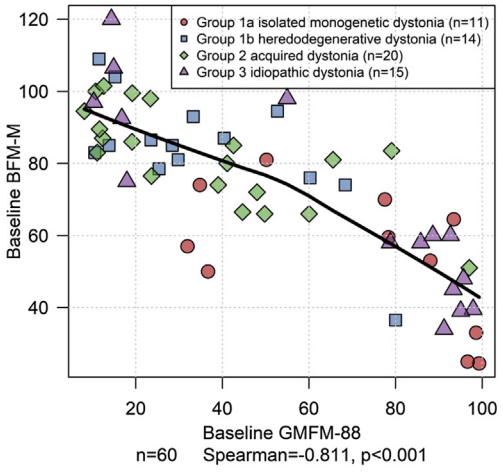

Fig. 3 – Relationship between baseline BFM-M and baseline GMFM-88.

of subtle signal change in GPi evident on MRI and significant co-morbidities commonly associated with this disorder[34] prompted some local debate as to how best to classify KT2MB dystonia. As more is learned about this newly identified genetic disorder, it is possible that re-classification of these KT2MB cases will be warranted.

DBS effects in heredodegenerative disorders are particularly challenging to evaluate, as temporary improvement, stabilisation, or alteration of the profile of regression may all reflect successful treatment. Further, carers may perceive meaningful improvement in quality of life, without reporting changes in the level of disability.[35] As reported by others,[10,36] this sub-group showed variable responses. At one year, four of 15 cases (cases 13,20,22,23) demonstrated improvement (4.9–38.5%) in GMFM-88 scores and three (cases 15,17,19) obvious deterioration (–11.7 - 20.3%) despite neuromodulation. No improvement in GMFM-88 or BFM-M was seen in the two cases with Lesch-Nyhan disease (cases 12,24), though families perceived meaningful improvement in individual goal areas (e.g. ease of handling during cares and transfers, reduced self-harming behaviours). Neither child with glutaric aciduria (cases 14,25) improved gross motor function or dystonia severity, as measured by the BMFM-M. Of the mitochondrial disorders, a child with Leigh disease (case 20) showed appreciable improvement in GMFM-88 scores, sustained over two years, without change in BFM-M, while two others (cases 16,19) continued to decline and failed to achieve gains in individual goal areas. In one child with PKAN

disease (case 22), a pronounced improvement in GMFM-88 & BFM-M scores at one year, associated with return of limited ambulation, had been lost by two years. Two others showed progressive decline despite DBS (cases 11,15) and one remained stable (case 18). It may be that lack of response to DBS is attributable to disease progression and/or concomitant impairments, such as weakness, spasticity and bradykinesia that are often present in these disorders. It is also possible that in some cases, despite apparently inexorable decline, DBS may be offering meaningful symptom control that only becomes evident with inadvertent or planned cessation of neuro-modulation.[37,38]

Overall, acquired dystonias (almost exclusively CP) failed to demonstrate improvement in GMFM-88 (or BFM-M) scores following DBS, though improvement is noted in some individuals. Half of the 18 dyskinetic CP cases with one-year GMFM-88 data showed clinically meaningful positive change in GMFM-88 scores. With reference to perceived magnitude of change scores outlined in the GMFM-88 manual[19] [p21] and detailed in the footnote[†] below, 2/18 cases (cases 31,45) made "medium positive" gains, 7/18 (cases 29,33,34,35,37,41,44) "small positive" gains, although in two of these cases the picture changed to one of decline from baseline GMFM-88 score at the two year follow up (cases 35,37). In one of these cases (case 35), the GMFM-88 score declined as a result of loss of floor sitting ability following bony hip surgery occurring between one and two years follow-up, highlighting the challenges controlling confounding factors over long term follow up. The biggest improvement (18–27%) was seen a child with kernicterus (case 45), which is concordant with other studies showing favourable DBS outcomes in dystonic CP caused by hyperbilirubinemia.[39,40] However, 3/22 cases (cases 27,38,40) failed to change, while six (cases 28,30,32,39,42,43) showed "small negative" changes in GMFM-88 score. The significant improvement in GMFM-88 at two years in the child with acquired brain injury (case 26) may be attributable to orthopaedic correction of equinovarus feet after DBS, though qualitative improvement in supported ambulation was emerging before orthopaedic intervention.

The heterogeneity of the CP population, which compromises a group of disorders of widely varying type, timing, location, and extent of brain injury, and the variability in response of CP subjects to even well-established interventions has been highlighted as a challenge in determining effective intervention for individual cases.[41] The basis for such individual variation in treatment response is not yet well understood. Given dystonia may be just one of multiple impairments in these children, it may be that gross motor response following DBS is inhibited by the influence of other impairments including spasticity, hypotonia (potentially unmasked following DBS), reduced selective movement control, orthopaedic deformity[42] and related surgical interventions, along with the effect of increasing body mass and limb inertia without concomitant improvement in muscle strength. Further, children with CP do not have a period of typical motor development before the onset of motor and non-motor difficulties, and also experience a longer proportion of life with dystonia than other subgroups. Disturbances in basal ganglia anatomy may compromise lead placement, even with the use of microelectrode recording and post-operative MR imaging,[13] resulting in technically sub-optimal delivery of DBS.[43] It is also possible that functional-structural re-arrangement of neural networks (i.e. inadequate connectivity within the cerebellar-basal-ganglia-thalamo-cortical loops[44] and issues with integrity of sensory pathways compromising sensory feedback following DBS[14]), and/or cellular dysmaturation,[45] may confer reduced responsiveness to DBS in this patient group, while the molecular level impact of genetic mutations on neuronal function are being increasingly recognised.[46] These numerous factors may potentially predispose to a disappointing motor response or it may be that a longer period is required before DBS confers gross motor function gains.

The published literature reports highly variable results for the efficacy of DBS in dyskinetic CP, with paediatric data largely limited to case studies and small case series.[7] In terms of gross motor outcome, we identified only a single published case study,[33] reporting an improvement of 37% in GMFM-88 score, though the reported score of 119 at follow up well exceeds the maximum possible GMFM-88 score of 100, raising questions about the integrity of this data. A meta-analysis of DBS, in predominantly adult subjects with dyskinetic CP, found a moderate improvement in the BFM-M (23.6%) and suggested that patients with higher preoperative BFM-M score (>85) have a greater risk of non-response to DBS.[29] Two other small studies,[13,39] although not evaluating gross motor function, report statistically significant group-level BFM-M improvement in children with CP. In contrast, like others,[47] we failed to demonstrate significant improvement in the BFM-M score in children with acquired dystonia. It is difficult to compare samples directly due to differences in inclusion criteria and mixed aetiologies in our sample, though baseline BFM-M scores highlight the severity of dystonia in our patient group, a factor that may predispose to disappointing outcomes. Our data does suggest, however, that expectations for significant gross motor function change following DBS should be tempered when goal setting for children with CP.

Results in idiopathic dystonias (group 3) are difficult to interpret given the highly heterogeneous clinical presentation of individuals comprising this group, and correspondingly highly variable outcome results. Although the majority of cases showed little change in GMFM-88 scores, a third of cases made significant gains in gross motor function. Three cases with additional features including cognitive impairment (cases 52,59) and specific language impairment (case 53), showed appreciable improvements, as did a child with juvenile onset dystonia parkinsonism of unknown cause (case 54). Of two other cases with dystonia parkinsonism, one remained stable (case 55), while the other continued to lose motor skills (case 57). The biggest improvement in GMFM-88 scores (>54%) was seen in case 58, who was recently found to have GNA01 mutation, which will result in this case being re-classified to group 1a for future analyses, further strengthening the DBS effect size in the 1a group. A qualitative review of group 3 data suggests a trend for poorer motor response in those with infantile onset of dystonia, which again may relate to the lack of

[†] Perceived magnitude of change: Absolute GMFM-88 change 7.0–24.5% = "medium positive"; 1.3–6.9% = "small positive"; −1.9–1.2% = "no change"; −2.0 to −7.8% = small negative".

a pre-established motor repertoire and underlying dysfunction of the cortex-basal ganglia network, such that reducing dystonia does not readily offer improved voluntary motor function. This also potentially argues for even earlier intervention with DBS in these cases, to coincide with the period when 'critical and sensitive windows of cerebral development and plasticity' are still open.[38,48,49] Future diagnostic progress will inevitably result in aetiological re-classification of some of these individuals, though the reality in clinical practice is that a significant proportion of cases presenting to DBS centres will not yet have a firm aetiological diagnosis on which to base prognostic discussions at the time of surgical goal setting.

It is important to note that the absence of gross motor (and/or BFM-M) improvement in some cases does not necessarily infer lack of meaningful response, as goals related to stabilisation of dystonia, improvements in manual function,[50] care, comfort and a range of other family-focused goal areas,[13,28,51] may still be achieved. It is also possible that, rather than the acquisition of new gross motor skills, DBS offers improvement in qualitative aspects of gross motor function and/or improves consistency of motor performance in some children. Additional measures of motor performance and function may be needed to capture such treatment effects.[52]

Limitations of our study should be acknowledged. This is a modest case series from a single centre using data collected during routine clinical practice. The sample is highly heterogeneous in a number of ways, including diagnosis, extent of brain involvement, co-morbidities, concomitant impairments, as well as baseline function and dystonia severity. The small overall and subgroup sample sizes limit the power of the study to detect significant differences, particularly when these are small, and precludes detailed subgroup analysis. Conversely, the pooling of different aetiologies for the purposes of analysis, and the inclusion of patients with complex mixed impairments, make it difficult to ascertain the extent to which individual aetiologies respond to DBS. Larger, more homogeneous samples could be helpful to determine DBS outcomes in specific aetiologies and better allow characterisation of the patient factors that facilitate DBS outcome. Although multi-centre collaboration is likely required to obtain adequately powered studies, this would also introduce further variation in terms of a greater disparity of baseline factors, differences in operative techniques, target selection and surgical timing, particularly given DBS surgery is limited to children over the age of seven years in some countries. Alternative methodology, such as N-of-1 Single Case Experimental Design (SCED) studies, with multiple baselines and follow-up points, replicated across numerous participants, may allow us to better capture relevant changes in this necessarily low-volume high-intensity area of clinical practice.[53] Such methodology may help correct for the lack of a comparison group not receiving DBS, which is potentially an issue due to the inability to control for confounding variables such as developmental maturation, allied health and surgical inputs, and dystonia medication in the present study. Length of follow up may also be an issue, particularly for individuals with disorders such as dyskinetic CP, in whom no foundation of gross motor function was developed before the onset of the movement disorder. One small study, involving adults with dyskinetic CP, found improvement stabilises around two years following DBS.[40] It is therefore possible a longer time course than used in our study is needed to adequately capture treatment effects. The risk of observer bias presented by lack of assessor blinding in this study is ameliorated somewhat by the use of a criterion-referenced assessment where "hands-on" assistance is prohibited. Reliability and validity of the GMFM-88 have been established for both CP and non-CP diagnoses.[19] The extent to which the GMFM-88 is reliable and sensitive to change in children with dystonic movement disorders is unknown, with day-to-day performance variability potentially creating "noise" that may mask treatment effects in these disorders. This presents another argument for N-of-1 SCED case series, allowing a mean baseline to be established at multiple time points before the intervention, and compared with a mean outcome at multiple clustered time-points following DBS. The GMFM-88 was utilised in this paper to allow comparison of results across a cohort of mixed aetiologies. It could be argued that the GMFM-66 would be preferable for the evaluation of CP cases, given its stronger psychometric properties.[19] However, the GMFM-66 is known to have significant floor effect in children with low motor ability, and to therefore be less useful when scoring children of low motor ability.[54] Given 16 of our 19 CP cases were GMFCS IV/V, the GMFM-88 is likely to be a more sensitive measure and more relevant for the cohort of children examined in this paper. We encountered issues with patients with both low and higher gross motor function capacity, presenting the potential for underestimation of DBS effects. The omission of cases unable to complete GMFM-88 at baseline means any subsequent improvement is not captured, while those with high baseline GMFM-88 test scores have little scope to improve following DBS. This has led to a change in our surgical assessment practice over time, with the GMFM-88 now largely reserved for children functioning at GMFCS level II-IV equivalent at baseline. This is on the basis that goals for DBS intervention in children at GMFCS levels I and V equivalent are unlikely to relate to improving foundational gross motor skills, and recognises ceiling/floor effect difficulties when applying the GMFM-88 to children at each end of the functional spectrum. Finally, rater reliability was not formally evaluated, with data gathered as part of routine clinical care and multiple raters inevitably involved over the course of long term follow up. Although formal training in the GMFM-88 is not a requirement for test use, the majority of assessments were conducted by the primary author (KT), who had formal GMFM training and more than five years experience utilising the GMFM clinically prior to involvement in the DBS program, with local criterion testing re-confirmed in 2005. One other rater (HG) received GMFM training before commencing data collection. Three other raters, new to the service, received on the job training and supervision in GMFM implementation and scoring, two passing local criterion testing. For one rater, data was excluded for three individual testing sessions due to erroneous scoring and data collection for the project was stopped in the interests of ensuring data integrity. Despite these limitations, in the complete absence of literature addressing this specific area, and in light of an emerging international focus on DBS in children with CP,[7,55] we believe these results will be of interest to clinicians in the field.

In conclusion, this preliminary study suggests gross motor response to DBS is similar in profile to literature reporting results using impairment-based dystonia rating scales. More consistent improvements were seen in inherited monogenetic ("primary") movement disorders, while highly variable, often disappointing, gross motor responses were found in acquired, heredodegenerative, and idiopathic dystonias.

Although aetiology is an important explanatory variable, greater knowledge is needed about the patient and intervention factors that may influence individual patient outcome and elucidate why DBS outcomes differ across individuals, particularly in children with acquired and heredodegenerative dystonias where patient selection and treatment efficacy remain topics of considerable debate.

Multiple research methodologies are needed to comprehensively characterise patients, intervention parameters, and outcomes over time, while cross-centre agreement on common data sets and data sharing arrangements would allow both larger, more homogeneous samples and meta-analysis of treatment outcomes.[41] Given individual heterogeneity of response, single case experimental design (SCED) research models may well be necessary to capture the extent to which DBS stabilises motor variability and alters underlying motor capacity, particularly in children with acquired dystonia. Future studies need to carefully consider factors such as the wide diversity in baseline motor capacity, individualised goal areas, and prognosis for response, carefully selecting measures that are relevant to the individual. Goal areas and objective measures are expected to differ appreciably, depending on baseline functional state and aetiology/prognosis, while the same increment of change may have very different impact in different individuals.[41] Further psychometric work is required to ensure measures are accurate, reliable and responsive to clinically important change when applied to paediatric movement disorders.[52] Nonetheless, until such information is available, we hope these preliminary results will be of interest to clinicians attempting to negotiate realistic goals for DBS neuromodulation in childhood dystonias.

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Conflict of interest

None declared.

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Appendix A. Supplementary data

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