ORIGINAL RESEARCH

Differential response to pallidal deep brain stimulation among monogenic dystonias: systematic review and meta-analysis

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ABSTRACT

Objective Genetic subtypes of dystonia may respond differentially to deep brain stimulation of the globus pallidus pars interna (GPi DBS). We sought to compare GPi DBS outcomes among the most common monogenic dystonias.

Methods This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis of Observational Studies in Epidemiology guidelines. We searched PubMed for studies on genetically confirmed monogenic dystonia treated with GPi DBS documenting pre-surgical and post-surgical assessments using the Burke–Fahn–Marsden Dystonia Rating Scale Motor Score (BFMMS) and Burke–Fahn–Marsden Disability Score (BFMDS). We performed (i) meta-analysis for each gene mutation; (ii) weighted ordinary linear regression analyses to compare BFMMS and BFMDS outcomes between DYT-*TOR1A* and other monogenic dystonias, adjusting for age and disease duration and (iii) weighted linear regression analysis to estimate the effect of age, sex and disease duration on GPi DBS outcomes. Results were summarised with mean change and 95% CI.

Results DYT-*TOR1A* (68%, 38.4 points; p<0.001), DYT-*THAP1* (37% 14.5 points; p<0.001) and NBIA/DYT-*PANK2* (27%, 21.4 points; p<0.001) improved in BFMMS; only DYT-*TOR1A* improved in BFMDS (69%, 9.7 points; p<0.001). Improvement in DYT-*TOR1A* was significantly greater than in DYT-*THAP1* (BFMMS −31%), NBIA/DYT-*PANK2* (BFMMS −35%; BFMDS −53%) and CHOR/DYT-*ADCY5* (BFMMS −36%; BFMDS −42%). Worse motor outcomes were associated with longer dystonia duration and older age at dystonia onset in DYT-*TOR1A*, longer dystonia duration in DYT/PARK-*TAF1* and younger age at dystonia onset in DYT-*SGCE*.

Conclusions GPi DBS outcomes vary across monogenic dystonias. These data serve to inform patient selection and prognostic counselling.

INTRODUCTION

Dystonia, defined as a condition characterised by sustained or intermittent muscles contractions causing abnormal, often repetitive, movements, postures or both, is a common movement disorder leading to generalised, segmental or focal impairment of motor activities and physiological postures.[1 2] It has been linked to over 200 genetic mutations leading to autosomal dominant, recessive and X-linked disorders.[3 4] Genetic dystonias may present with variable age at onset, body distribution, temporal pattern and associated features.[1] Clinically, they are classified into 'isolated dystonias', such as DYT-*TOR1A*, childhood-onset foot dystonia followed by generalisation, and DYT-*THAP1*, adolescent-onset cranio-cervical dystonia; 'combined dystonias', such as DYT-*SGCE*, in which dystonia is 'combined' with myoclonus; and 'complex dystonias' such as NBIA/DYT-*PANK2*, a childhood-onset or adolescent-onset dystonia due to pantothenate kinase-associated neurodegeneration with brain iron deposition (PKAN).[3]

Deep brain stimulation (DBS) of the globus pallidus pars interna (GPi) is one of the most effective treatments for chronic, medically intractable, dystonia. Multiple trials have demonstrated that GPi DBS is safe and effective for patients with isolated generalised and segmental dystonia.[5 6] Outcomes after GPi DBS, however, can have variable success, which highlights the importance of patient selection. Narrative reviews have summarised data with divergent conclusions on the variables affecting GPi DBS outcomes.[4] Established predictors include electrodes location,[7] age at dystonia onset,[8] disease duration prior to GPi DBS[9] and whether fixed postures have complicated the phenotype.[10]

DYT-*TOR1A* patients with segmental or generalised dystonia are considered optimal candidates for surgery,[4 11] but no trial data are available to assess whether the outcomes on DYT-*TOR1A*-positive patients are comparable to those of patients with alternative genetic mutations. We sought to evaluate the differential extent to which monogenic dystonias respond to GPi DBS using a systematic review and meta-analysis of outcomes with data from published clinical trials, observational studies, case series and case reports.

METHODS

Search methods

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses and the Meta-analysis of Observational Studies in Epidemiology

guidelines.[12 13] We searched PubMed for interventional and non-interventional studies prior to January 1, 2019 reporting data on GPi DBS-treated patients screened for monogenic forms of dystonia using the following searching terms: 'deep brain stimulation', 'mutation', 'gene', 'genetics', 'inherited', 'familial', 'dystonic' and 'dystonia' (search string: '((Deep brain stimulation AND (dystonia OR dystonic) AND (mutation OR gene OR genetics OR inherited OR familial)))').

Abstracts and full-text articles were independently reviewed for eligibility criteria by four authors (CAA, AR, LM and SB). Duplicated studies were identified and excluded. Only studies referring to human subjects and published in English were considered. No restrictions were applied to sex, age, ethnicity, follow-up duration, disease duration, disease severity or type of dystonia. The reference list of each article was searched to screen for additional pertinent studies not captured by the original search strategy.

Inclusion and exclusion criteria

We included studies with cases of genetically confirmed dystonias treated with GPi DBS, with a minimum post-surgical follow-up of 3 months, and with Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) scores before and ≥3 months after GPi DBS.[14] Studies of patients with pooled rather than segregated genetic subtyping were excluded, as well as studies with assumed but not confirmed genetic data or incomplete follow-up.

Data extraction

We used a standardised data collection form to extract, from the BFMDRS, the Motor (BFMMS) and Disability Scores (BFMDS) before (baseline), at 3–24 months (short-term post-GPi DBS follow-up), and, when available, at >24 months (long-term follow-up). Additional data extracted included sample size, genetic mutations evaluated, year of publication, study design, age at disease onset, age at GPi DBS surgery and follow-up duration in months. Data were expressed as mean with SD. If two or more studies reported data from the same population, we included the most recent publication with the longest follow-up. In addition, if a study provided data on multiple genetic populations we allocated each to their corresponding dataset.

Assessment of risk of bias

Two investigators (CAA and AR) independently performed the quality appraisal of qualifying studies, which were rated as 'good', 'fair' or 'poor' as per the National Heart, Lung, and Blood Institute tools (Research Triangle Institute International. National Heart, Lung, and Blood Institute Quality Appraisal Tools) according to Cochrane handbook recommendations (see online supplementary figure 1).[15] Only studies with a 'good' or 'fair' rating were included in the analyses. Visual inspection of funnel plots was also conducted to assess for publication bias.[16]

Study aims and statistical analysis

We sought to analyse motor (BFMMS) and disability (BFMDS) outcomes of patients with confirmed monogenic dystonias treated with GPi DBS and to examine the impact of disease duration prior to GPi DBS, age, and sex. The following sets of analysis were conducted:

1. To analyse the effect of genetic mutations on GPi DBS outcomes, we performed a meta-analysis of BFMMS and BFMDS short-term and long-term results for each gene separately. This analysis was performed for at least two studies on a defined monogenic dystonia cohort with a sample size ≥5 patients each containing pre-GPi DBS and post-GPi DBS BFMDRS scores. The mean change between pre-intervention and post-intervention along with pooled SD (PSD) for each study was computed. Pearson's correlation coefficient between pre-value and post-value per gene mutation was estimated and used for computing PSD. Given the sample size, the inclusion of observational studies, and the heterogeneity across the studies, the pooled effect size was computed using a random effects model with DerSimonian and Laird method.[17] The heterogeneity across the studies was measured using the I^2 statistic. An I^2 statistic >50% was considered as representing substantial heterogeneity.[15] The results of the meta-analysis were summarised using I^2 statistic, per cent relative improvement, pooled mean difference along with a 95% CI and p value for each specific gene mutation separately for each outcome. Meta-analysis was conducted separately for short-term and long-term outcomes and results were summarised using forest plots.
2. To analyse the outcomes of genetic mutations compared with DYT-*TOR1A*, we performed unadjusted and adjusted (age at dystonia onset and dystonia duration at surgery) comparisons of BFMMS and BFMDS between DYT-*TOR1A* and other distinct forms of monogenic dystonia. This analysis was performed when at least two studies, one of which with a sample size >1 patient, were available. We performed unadjusted and adjusted weighted ordinary linear regression analyses with robust variance estimation using Huber and Sandwich approach. The weight was assigned according to the sample size of each study. Larger sample size studies received relatively large weights compared with small sample size studies. After regression analysis, unadjusted paired-wise comparisons were performed across all gene mutations. The results of regression analyses were displayed using regression coefficient, 95% CI and p value. In the adjusted analysis, age and disease duration were adjusted irrespective of their significance levels.
3. To analyse the effect of age at dystonia onset, disease duration at surgery and sex on GPi DBS outcomes, we used weighted linear regression analyses with robust variance estimation after adjusting for gene differences and separately for each gene. This analysis was performed for each monogenic dystonia when at least two studies were identified from the systematic review of the literature.

Continuous data were summarised using mean and SD; categorical data with frequencies and proportions. All the statistical analyses were carried out using STATA V.15.1. P values less than or equal to 5% were considered statistically significant results.

RESULTS

Of 165 studies, 87 met full criteria and underwent data extraction (see online supplementary table 1), individual quality assessment and evaluation of the risk of bias (figure 1). In all, 34 articles met criteria for meta-analysis yielding 36 datasets and a sample size of 311 patients distributed in DYT-*TOR1A* (n=269), DYT-*THAP1* (n=16) and NBIA/DYT-*PANK2* (n=26) mutations. In total, 81 articles met criteria for the analysis of outcomes vs DYT-*TOR1A*, providing 87 datasets and a sample size of 432 patients in DYT-*TOR1A* (n=306), DYT-*THAP1* (n=24), NBIA/DYT-*PANK2* (n=40), DYT/PARK-*TAF1* (n=23), *ACTB* (n=3), CHOR/DYT-*ADCY5* (n=3), *GNAO1* (n=8) and DYT-*SGCE* (n=25) mutations. In addition, individual datasets of single case reports (n=13) were extracted from seven studies reporting data on DYT/PARK-*GCH1*, CHOR-*VPS13A*, DYT-*SGCE*

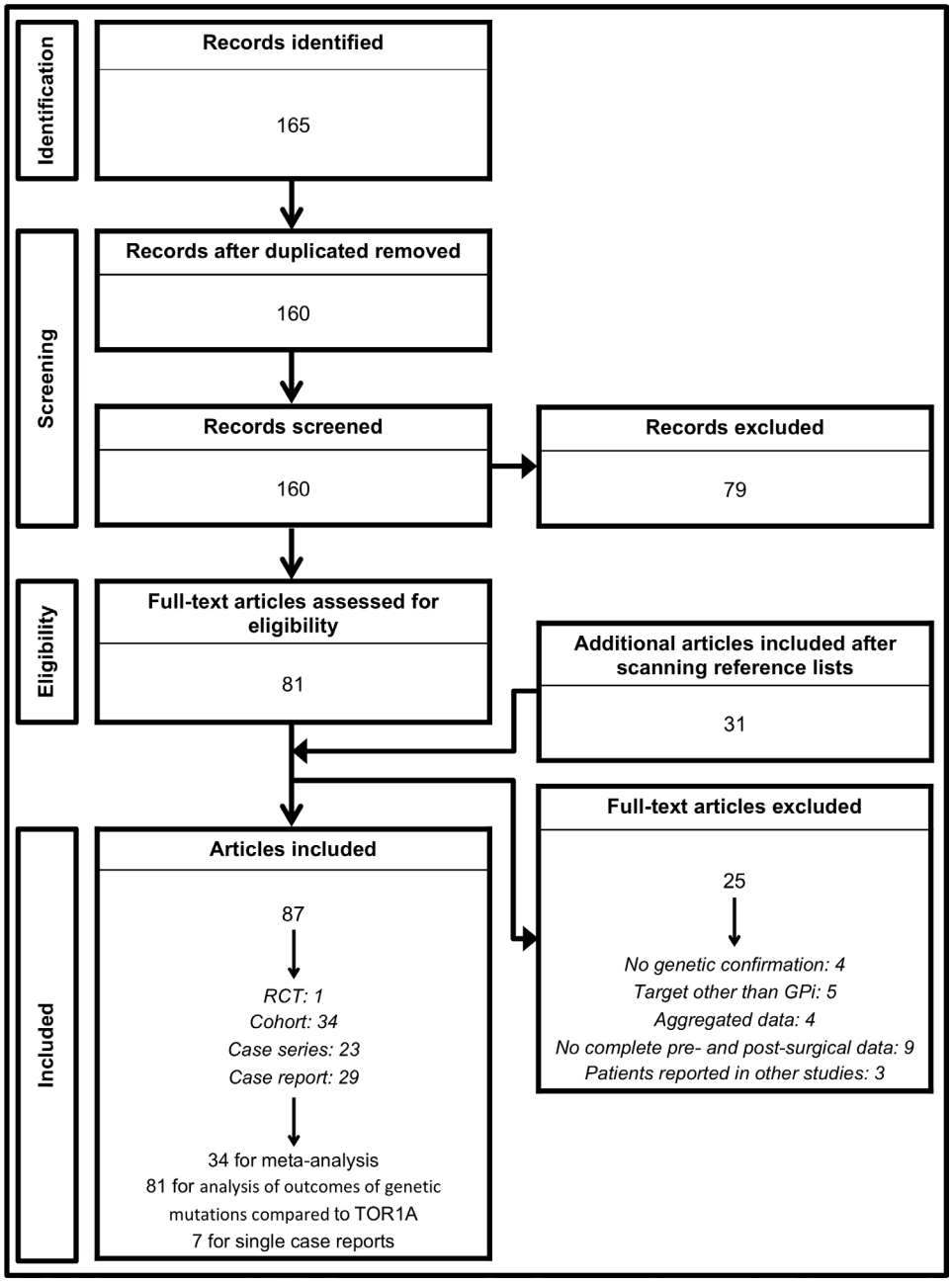

Figure 1 Study flow chart phases of the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram recommendations. RCT, randomised clinical trial.

+ DYT-*TOR1A*, DYT/PARK-*ATP1A3*, DYT-*PRKRA*, DYT/PARK-*GLB1*, NBIA/DYT-*DCAF17*, trisomy X, SCA-*ATXN3*, SCA-*ATXN2*, PxMD-*SLC2A1* and *ATM* (figure 1, online supplementary table 2). Demographic data are reported in table 1.

Meta-analysis

Motor endpoint (BFMMS)

In the short term (11.8±3.6 months; range: 6–12), BFMMS improved by 68% in DYT-*TOR1A* (−38.4, p<0.001), 37% in DYT-*THAP1* (−14.5, p<0.001) and 27% in NBIA/DYT-*PANK2* (−21.4, p<0.001). Long-term (46.6±16.4 months; range: 24–72) BFMMS data were available for DYT-*TOR1A*, showing sustained improvement (68%, −37.1, p<0.001) (figure 2).

Disability endpoint (BFMDS)

In the short term (12.5±2.9 months; range: 10–24), BFMDS improved by 69% in DYT-*TOR1A* (−9.7, p<0.001) but not in DYT-*THAP1* (−0.4; p=0.895) or NBIA/DYT-*PANK2* (0; p=0.993). Long- term (45.9±18.5 months; range 25–72) BFMDS data were available for DYT-*TOR1A*, showing sustained improvement (68%, −10; p<0.001) (figure 3).

Comparison of GPi DBS effect on monogenic dystonias

Motor endpoint (BFMMS)

DYT-*TOR1A* was associated with greater motor improvement than DYT-*THAP1* (−31%; p<0.001), NBIA/DYT-*PANK2* (−35%; p=0.016) and CHOR/DYT-*ADCY5* (−36%; p<0.001).

Table 1 Demographic and clinical data of included patients

Mutations	Age at dystonia onset (years)	Sex (% of female)	Disease duration at GPi DBS (years)
DYT-*TOR1A* (n=306)	9.3±2.9	62±26	12.1±8.3
DYT/PARK-*TAF1* (n=23)	39.7±9.5	0	4.1±3.4
DYT-*THAP1* (n=24)	10.2±4.9	40±35	18.4±10
DYT-*SGCE* (n=25)	5.8±5.4	74±29	24.8±14.7
NBIA/DYT-*PANK2* (n=40)	12.6±8.8	56±35	9.3±2.7
CHOR/DYT-*ADCY5* (n=3)	2.5±2.1	80±20	10.8±4
GNAO1 (n=8)	3.1±1.9	67±47	4.4±1.2
ACTB (n=3)	14.7±3.9	100	7

Data are expressed as mean±SD.
GPi DBS, deep brain stimulation of the globus pallidus pars interna; n, number of patients included; N/A, not available.

We found no significant differences between DYT-*TOR1A* and DYT/PARK-*TAF1*, DYT-*SGCE*, *GNAO1* and *ACTB* (figure 4).

Disability endpoint (BFMDS)

DYT-*TOR1A* was associated with greater reduction in disability than NBIA/DYT-*PANK2* (−53%; p=0.004) and CHOR/DYT-*ADCY5* (−42%; p=0.003). We found no significant differences between DYT-*TOR1A* and DYT/PARK-*TAF1*, DYT-*THAP1*, DYT-*SGCE*, *GNAO1* and *ACTB* (figure 4).

Effect of disease duration, age at onset and sex on GPI DBS outcome

Longer dystonia duration prior to GPi DBS was associated with worse motor outcome in DYT-*TOR1A* (p=0.040) and DYT/PARK-*TAF1* (p=0.001), but not in DYT-*THAP1*, DYT-*SGCE* and NBIA/DYT-*PANK2* (Table 2, Supplementary Figure 2). Older age at dystonia onset was associated with worse motor outcome in DYT-*TOR1A* (p<0.001) but not in DYT/PARK-*TAF1*, DYT-*THAP1* and NBIA/DYT-*PANK2*, and better outcome in DYT-*SGCE* (p=0.010) (table 2).

Sex was not associated with GPi DBS outcomes in DYT-*TOR1A*, DYT-*SGCE* and NBIA/DYT-*PANK2*. In DYT-*THAP1*, there was a trend towards better GPi DBS motor outcomes in women compared with men (p=0.051) (table 2).

Analysis of single cases or rarer dystonia-associated mutations

There was improvement in motor and disability outcomes reported in single cases of DYT/PARK-*GCH1* (−44.5% BFMMS; −85.7% BFMDS), CHOR-*VPS13A* (−75% BFMMS; −50% BFMDS) and DYT-*SGCE* + DYT-*TOR1A* mutations (−83.3% BFMMS; −75% BFMDS); in motor outcomes in DYT/PARK-*ATP1A3* (−26.1% and −7% BFMMS), DYT-*PRKRA* (−74.4% BFMMS), DYT/PARK-*GLB1* (−20% BFMMS), NBIA/DYT-*DCAF17* (−42.0% BFMMS; −7.7% BFMDS), trisomy X (−44.2% BFMMS) and SCA-*ATXN3* (−10% BFMMS;+33% BFMDS); and worsening of motor and disability outcomes in SCA-*ATXN2* (+35.5% BFMMS;+112.5% BFMDS), PxMD-*SLC2A1* (+2.6% BFMMS) and *ATM* (+13.0% BFMMS;+12.5% BFMDS) (table 3).

DISCUSSION

We confirmed the beneficial effect of GPi DBS on motor and disability outcomes in DYT-*TOR1A*, DYT-*THAP1* and NBIA/DYT-*PANK2* cases, with a greater improvement in DYT-*TOR1A* compared with other monogenic dystonias. Differential improvement was observed in *ACTB*, *GNAO1*, DYT-*SGCE*, DYT/PARK-*TAF1* and CHOR/DYT-*ADCY5*, affected negatively by longer disease duration prior to GPi DBS (DYT-*TOR1A* and DYT/PARK-*TAF1*) and older age at dystonia onset (DYT-*TOR1A*; the opposite for DYT-*SGCE*).

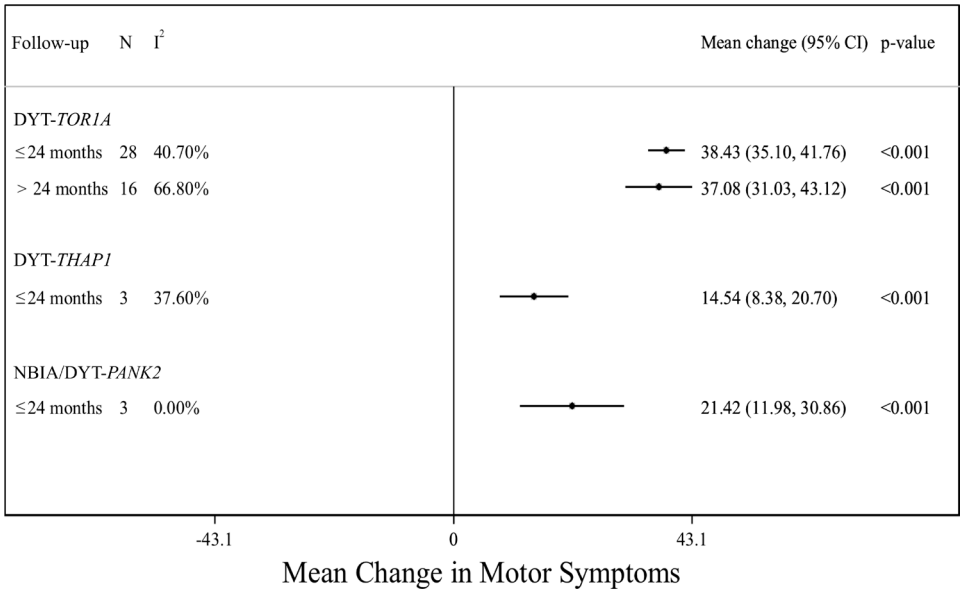

Figure 2 Forest plot-motor endpoints. Forest plot of the motor endpoints obtained by the meta-analysis of the following genetic dystonias: DYT-*TOR1A*, DYT-*THAP1* and NBIA/DYT-*PANK2*. Data presented refer to absolute change of the BFMMS. n=number of datasets included. BFMMS, Burke–Fahn–Marsden Dystonia Rating Scale Motor Score.

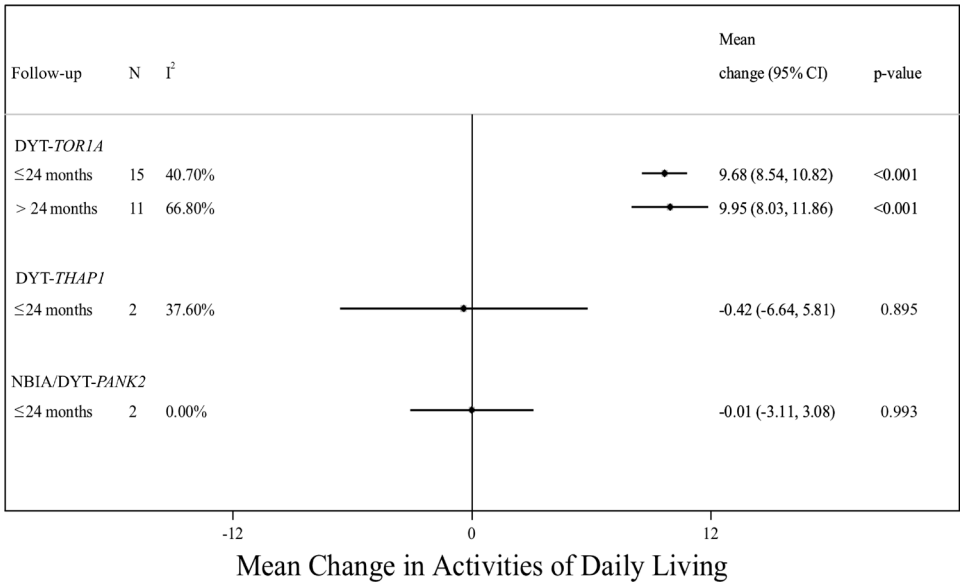

Figure 3 Forest plot-disability endpoints. Forest plot of the disability endpoints obtained by the meta-analysis of the following genetic dystonias: DYT-*TOR1A*, DYT-*THAP1* and NBIA/DYT-*PANK2*. Data presented refer to absolute change of the BFMDS. n=number of datasets included. BFMDS, Burke–Fahn–Marsden Disability Score.

Previous studies alternatively suggested that dystonia duration before surgery may or may not predict outcome after GPi DBS.[5 8 18–22] In agreement with a recent meta-regression analysis reporting an association between shorter dystonia duration and greater GPi DBS motor improvement in patients with isolated dystonia,[9] we found that monogenic dystonias DYT-*TOR1A* and DYT/PARK-*TAF1* may benefit from an earlier surgical treatment. This result is in accordance with previous findings indicating that an early modulation of dystonia-associated cortical plasticity might slow or prevent progression.[19] Our findings suggest that different genetic mutations may account for a different impact of disease duration on GPi DBS outcome, and similar results emerged from the analysis of age at dystonia onset, with younger DYT-*TOR1A* and older DYT-*SGCE* patients benefiting most from GPi DBS. Also, there was a trend towards better motor outcomes in women compared with men in DYT-*THAP1*.

GPi DBS demonstrated short-term and long-term efficacy in DYT-*TOR1A*,[3 4] and a lower but also significant improvement in DYT-*THAP1* and NBIA/DYT-*PANK2*.[23 24] The differential extent of motor benefit observed in DYT-*TOR1A* and DYT-*THAP1* might reflect the differential pattern of metabolic abnormalities reported by connectivity studies in these two monogenic forms of dystonias,[25 26] as well as the older age at onset of DYT-*THAP1* and its predominant axial and cranio-cervical distribution,[27]

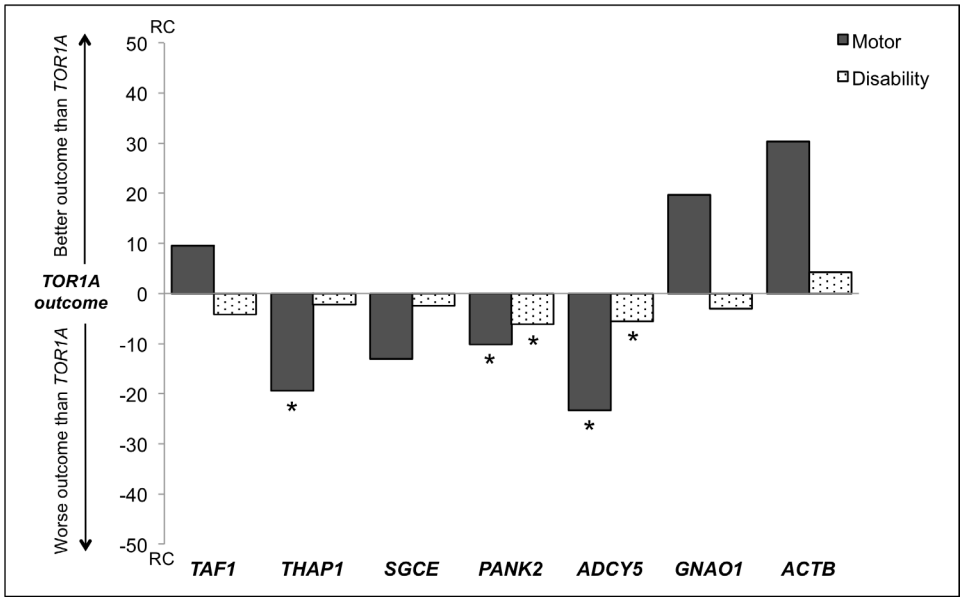

Figure 4 Comparison of GPi DBS outcomes between DYT-*TOR1A* and other monogenic forms of dystonia Motor outcomes were assessed by the score of the Burke–Fahn–Marsden Dystonia Rating Scale; disability outcomes by the disability Burke–Fahn–Marsden Dystonia Rating Scale. GPi DBS: deep brain stimulation of the globus pallidus pars interna. RC: regression coefficient after adjusting for age and disease duration. *Indicates significant difference compared with DYT-*TOR1A*.

Table 2 Effect of disease duration, age and sex on GPI DBS outcome

Motor endpoint					Disability endpoint			
Type of dystonia	Regression coefficient	95% CI		P value	Regression coefficient	95% CI		P value
Disease duration					**Disease duration**			
DYT-*TOR1A*	−0.7	−1.4	−0.1	0.040*	−0.1	−0.4	0.2	0.488
DYT/PARK-*TAF1*	−4.3	−5.9	−2.7	0.001*	N/A	N/A	N/A	N/A
DYT-*THAP1*	−0.3	−1.4	0.9	0.566	−0.6	−3.7	2.5	0.251
DYT-*SGCE*	0.2	−0.3	0.6	0.428	0.1	−0.3	0.4	0.717
NBIA/DYT-*PANK2*	−2.7	−9.5	4.1	0.354	0.2	−2.8	3.1	0.867
Age at dystonia onset					**Age at dystonia onset**			
DYT-*TOR1A*	−5.3	−7.4	−3.2	<0.001*	−0.1	−1.7	1.6	0.910
DYT/PARK-*TAF1*	−0.7	−3.4	2.1	0.586	N/A	N/A	N/A	N/A
DYT-*THAP1*	−1.4	-6	3.3	0.456	N/A	N/A	N/A	N/A
DYT-*SGCE*	0.8	0.2	1.4	0.010*	0.1	−0.4	0.6	0.515
NBIA/DYT-*PANK2*	0.1	−1.3	1.4	0.925	0.5	−0.6	1.7	0.246
Sex (proportion of females)					**Sex (proportion of females)**			
DYT-*TOR1A*	2.1	−27.8	31.9	0.883	4.0	−4.2	12.2	0.295
DYT-*THAP1*	12.0	−0.1	24.1	0.051	N/A	N/A	N/A	N/A
DYT-*SGCE*	−18.9	−53.9	16.2	0.236	10.3	−62.9	83.5	0.324
NBIA/DYT-*PANK2*	38.7	−81.5	158.8	0.381	1.9	−17.5	21.4	0.709

*Indicates significant p value.
N/A, not applicable.

which have been reported as factors negatively influencing GPi DBS outcome.[28] The lower extent of motor benefits observed in NBIA/DYT-*PANK2* might result from the high variability in associated features (eg, spasticity) of the PKAN phenotype.[29]

Available data were insufficient for a meta-analysis in cases of DYT/PARK-*TAF1*, associated with X-linked dystonia-parkinsonism (XDP or Lubag disease)[30]; DYT-*SGCE*, responsible for an early-onset form of myoclonus-dystonia predominantly involving the neck and arms[3]; CHOR/DYT-*ADCY5*, which may cause a variable phenotype characterised by chorea, dystonia or myoclonus[31 32]; *GNAO1*, associated with a form of childhood dystonia combined with other hyperkinetic movement disorders, cognitive impairment and seizures[33]; and *ACTB*, responsible for a clinical phenotype characterised by dystonia and deafness.[34 35] However, outcomes may not be significantly different from those observed in DYT-*TOR1A* using age- and disease-duration-adjusted motor and disability outcomes, with the only exception of CHOR/DYT-*ADCY5* that showed significantly lower benefits from GPi DBS than DYT-*TOR1A*.

The cases of DYT/PARK-*TAF1* treated with GPi DBS (n=23) showed good motor and disability improvement at 12 months. While these outcomes are encouraging, it is important to note that the clinical picture associated with DYT/PARK-*TAF1* (ie, XDP) may change over time. Focal dystonia tends to generalise within the first 5 years; after 10 years, dystonia becomes relatively less severe in the face of increasingly prominent parkinsonian signs.[30]

Table 3 Single case analysis

Articles	Mutation	N of patients	Sex (M/F)	Age at dystonia onset	Disease duration at DBS	Pre-surgical BFMMS	Post-surgical BFMMS (months after DBS)	Pre-surgical BFMDS	Post-surgical BFMDS (months after DBS)
Beaulieu-Boire *et al* (2016)	DYT/PARK-*GCH1*	1	0/1	7	59	18	10 (12 m)	7	1 (12 m)
Beaulieu-Boire *et al* (2016)	CHOR-*VPS13A*	1	1/0	22	9	14	14.5 (12 m) 3.5 (45 m)	16	8 (12 m)
Wang *et al* (2017)	DYT-*SGCE* +DYT-*TOR1A*	1	1/0	12	18	21	3.5 (6 m)	16	4 (6 m)
Kamm *et al* (2008)	DYT/PARK-*ATP1A3*	1	1/0	12	12	55.5	41 (12 m)	NA	NA
Brucke *et al* (2014)	DYT/PARK-*ATP1A3*	1	1/0	17	5	28	26 (12 m)	NA	NA
Koy *et al* (2016)	DYT-*PRKRA*	1	NA	NA	NA	92	25 (12 m) 23.3 (48 m)	NA	NA
Roze *et al* (2016)	DYT/PARK-*GLB1*	1	0/1	16	8	70	56 (12 m)	NA	NA
Beaulieu-Boire *et al* (2016)	NBIA/DYT-*DCAF17*	1	0/1	16	8	50	27 (12 m) 29 (18 m)	13	12 (12 m) 14 (18 m)
Beaulieu-Boire *et al* (2016)	Trisomy X	1	0/1	6	11	52	29 (5 m)	12	12 (12 m)
Beaulieu-Boire *et al* (2016)	SCA-*ATXN3*	1	0/1	44	3	20	18 (12 m)	6	4 (12 m)
Beaulieu-Boire *et al* (2016)	SCA-*ATXN2*	1	0/1	39	4	15.5	21 (12 m) 21 (36 m)	4	11 (12 m) 8.5 (36 m)
Hanci *et al* (2018)	PxMD-*SLC2A1*	1	0/1	25	19	56.5	58 (108 m)	NA	NA
Beaulieu-Boire *et al* (2016)	*ATM*	1	1/0	1	10	69	100.5 (12 m) 78 (33 m)	24	28 (12 m) 27 (33 m)

BFMDS, Burke–Fahn–Marsden Dystonia Rating Scale - Disability score; BFMMS, Burke–Fahn–Marsden Dystonia Rating Scale - Motor score; M/F, males/females; NA, not available.

A recent observational study from 16 patients showed that GPi DBS may also improve the parkinsonian features associated with XDP.[36] Favouring earlier timing at surgery, the authors observed an association between less atrophy in the caudate nucleus and better GPi DBS clinical outcomes.[36]

In DYT-*SGCE*, GPi DBS has been reported to benefit both the myoclonus and the dystonia.[37 38] Our analysis of 26 patients with DYT-*SGCE* showed a significant improvement on motor and disability outcomes similar to those observed in DYT-*TOR1A*, thus confirming that GPi DBS may be an optimal therapeutic option for carriers of DYT-*SGCE*-associated dystonia. *GNAO1* patients treated with GPi DBS (n=8) showed mixed results likely related to the heterogeneous clinical presentation of this particular genotype, which is frequently associated with a progressive encephalopathy. GPi DBS seems a viable (palliative) option for cases with extreme dystonia severity with difficulties in feeding and/or life-threatening clinical conditions.[39] *ACTB* patients (n=3) showed good preliminary results, which suggest the potential for GPi DBS as a therapeutic option for this particular form of dystonia but also warrant further evaluation due to the limited number of cases reported to date. Finally, the analysis of the few CHOR/DYT-*ADCY5* cases (n=3) treated with GPi DBS suggested lower clinical efficacy than DYT-*TOR1A*. However, it should be considered that combined (DYT-*SGCE*, DYT/PARK-*TAF1*, CHOR/DYT-*ADCY5*) and complex (*GNAO1*, *ACTB*) dystonias present with a plethora of accompanying neurological features, which may or may not respond to GPi-DBS. The greater clinical benefit observed in DYT-*SGCE* could be explained by the effect of GPi-DBS on both dystonia and myoclonus.[40] The limited efficacy observed in *GNAO1* may be explained by the concomitance of features characteristically not responsive to GPi-DBS, such as intellectual disability and drug-resistant seizures.[39]

GPi DBS in monogenic dystonias confined to single case reports yielded results ranging from excellent (DYT/PARK-*GCH1*, CHOR-*VPS13A* and DYT-*SGCE* +DYT-*TOR1A*), mild/moderate (DYT/PARK-*ATP1A3*, DYT-*PRKRA*, DYT/PARK-*GLB1*, NBIA/DYT-*DCAF17* and trisomy X), to futile (SCA-*ATXN3*, SCA-*ATXN2*, PxMD-*SLC2A1* and *ATM*). The significant variability observed in these rare forms of dystonia highlights the critical need for prospective clinical registries reporting all cases of genetically defined dystonia treated with GPi DBS. For DYT/PARK-*ATP1A3*, there are only few reports with results ranging from moderate to no improvement after GPi DBS.[41 42] Also, we found 13 cases of DYT-*KMT2B*, an emerging form of childhood onset, generalised dystonia with prominent cervical, cranial and laryngeal involvement.[43 44] While these patients had a variable extent of dystonia improvement after GPi DBS, sometimes with 'dramatic' amelioration in walking, scoliosis and dysphonia,[44] none of them received pre-surgical versus post-surgical evaluations with validated clinical scales. Therefore, we could not include them in this analysis.

Some limitations should be considered in the interpretation of our results. First, the limited number of cases limited the possibility of extending the meta-analysis beyond DYT-*TOR1A*, DYT-*THAP1* and NBIA/DYT-*PANK2*. Second, the small number of cases available and heterogeneous clinical presentation of *GNAO1*, *ACTB* and CHOR/DYT-*ADCY5* precludes the generalisability of our findings to the entire spectrum of clinical phenotype associated with these rare subtypes of monogenic dystonias. Third, we lacked patient-centred outcome measures, such as quality of life, which are critical to provide a comprehensive analysis of GPi DBS outcomes. Fourth, only few studies reported data on the accuracy of DBS lead placement. Thus, results could not be adjusted for this important clinical variable. Fifth, the lack of randomised clinical trials or blind prospective observational studies inevitably limited the strength of the data available for analyses. Finally, the effects of DBS on targets other than GPi, such as the subthalamic nucleus, could not be investigated due to paucity of data.

These limitations notwithstanding, this study provides robust support for both short-term and long-term efficacy of GPi DBS in DYT-*TOR1A*, a modest but still significant improvement in DYT-*THAP1* and NBIA/DYT-*PANK2* patients, and promising but preliminary results for dystonia associated with DYT-*SGCE*, DYT/PARK-*TAF1*, *ACTB* and *GNAO1* mutations. We also confirmed that dystonia duration prior to surgery and age at dystonia onset may differentially affect GPi DBS motor outcome in patients with DYT-*TOR1A*, DYT/PARK-*TAF1* and DYT-*SGCE* mutations. We suggest that genetic testing should be employed in dystonia cases being considered for GPi DBS. Prospective clinical registries will be required to confirm these findings and further clarify the role of GPi DBS in patients with rare genetic forms of dystonia.

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