REVIEW

Deep brain stimulation for dystonia

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ABSTRACT

The few controlled studies that have been carried out have shown that bilateral internal globus pallidum stimulation is a safe and long-term effective treatment for hyperkinetic disorders. However, most recent published data on deep brain stimulation (DBS) for dystonia, applied to different targets and patients, are still mainly from uncontrolled case reports (especially for secondary dystonia). This precludes clear determination of the efficacy of this procedure and the choice of the 'good' target for the 'good' patient. We performed a literature analysis on DBS for dystonia according to the expected outcome. We separated those with good evidence of favourable outcome from those with less predictable outcome. In the former group, we review the main results for primary dystonia (generalised/focal) and highlight recent data on myoclonus-dystonia and tardive dystonia (as they share, with primary dystonia, a marked beneficial effect from pallidal stimulation with good risk/benefit ratio). In the latter group, poor or variable results have been obtained for secondary dystonia (with a focus on hereditary degenerative and metabolic disorders). From this overview, the main results and limits for each subgroup of patients that may help in the selection of dystonic patients who will benefit from DBS are discussed.

INTRODUCTION

Attempts to treat dystonia with functional surgery started in the early 50s with lesions in various sites, including dentate nucleus, zona incerta, subthalamic nucleus and the two most common and most effective targets, the pallidum interna (GPi) and the thalamus. Partial to marked improvements were obtained, but the benefits were not always sustained and there was a risk of permanent disability. Deep brain stimulation (DBS) for dystonia was first described by Mundinger in 1977,¹ Benabid *et al* in 1987,² Krauss *et al*³ and Kumar *et al*⁴ in 1999, and Coubes *et al*⁵ in 2000. A large number of patients have been successfully treated since then, but interpretation of the literature remains difficult because of differences across teams in terms of methodology (including surgical protocol), stimulation settings, evaluation and follow-up. Beyond technical considerations, the criteria for selection of patients, the age at the time of surgery, and the diversity and complexity of dystonia subtypes are also highly variable. This may account (at least partially) for the striking variability in responsiveness to DBS. The outcome of surgery in individual patients is hard to predict, particularly in the focal or secondary dystonias. Firm consensual recommendations for patient selection have been impossible to establish, except in a few situations, including

generalised primary dystonia and severe cervical dystonia. The efficacy and safety of GPi-DBS have been well established in generalised⁶ or segmental^{7,8} primary dystonia in large, well-designed multicentre trials. In addition to these primary dystonias, GPi-DBS has recently been demonstrated to be markedly effective in myoclonus-dystonia and tardive dystonia.⁹ In sharp contrast, the benefit of GPi-DBS for the secondary dystonias (such as dystonia-choreoathetosis cerebral palsy or inherited metabolic disorders) is still subject to debate. In order to help the clinician select the 'good' target for the 'good' patient at the right time with the best risk/benefit ratio, we have reviewed the published literature, focusing on patient outcome, and separated the subtypes of dystonia with good predictive factors,¹⁰ which are most likely to produce good improvement including better quality of life, from those with less predictable or less favourable outcome.

METHODS

The PubMed database was searched for articles describing DBS for dystonia. Keywords were 'dystonia', 'DBS', 'choreoathetosis', 'cerebral palsy' pallidum, GPi, thalamus and subthalamic nucleus. Only publications written in English and reporting individual clinical outcome data were included in the review. When patients were mentioned in multiple overlapping publications, we compiled the data for the same patient and mentioned it in the table. Instead of following the classical dichotomy between primary and secondary dystonia, we chose to present the literature analysis according to the expected outcome (decision-making support). We separated those with good evidence of favourable outcome from those with less predictable outcome. Dystonia with features of parkinsonism were excluded. Dystonia subtypes are primary, dystonia plus (dystonia-parkinsonism was excluded) and secondary dystonia (with focus on tardive dystonia, status dystonicus and dystonia-choreoathetosis cerebral palsy). In primary dystonia, results are reported according to body distribution (generalised, segmental/cervical and cranial).

LITERATURE ANALYSIS ACCORDING TO THE EXPECTED OUTCOME**Dystonia with good evidence of favourable outcome**

This group is heterogeneous and includes primary dystonia, myoclonus-dystonia (dystonia-plus syndrome category) and tardive dystonia (secondary dystonia category). Improvements of 50–60% were generally observed, with some patients experiencing as much as a 90% reduction in severity and

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disability on the Burke–Fahn–Marsden (BFM) dystonia scale with concomitant improvement in the quality of life. Beyond their differences, these different types of dystonia share the common feature of being ‘functional’ (eg, non-lesional) in contrast with secondary lesional dystonia, the latter often having abnormal MRI scans.

Specificities, long-term follow-up and predictive factors of outcome (if known) are detailed for each type of dystonia (primary dystonia, myoclonus-dystonia and tardive dystonia).

Primary dystonia

Generalised and segmental/cervical dystonia

To date, experience with GPi stimulation has been reported in more than 200 patients with primary dystonia in reviews,^{9–16} for patients with *DYT1* mutations,^{5–7 13 14 17–25 16} and in primary dystonias of unknown origin.^{6 7 19 20 26–29} In generalised^{6 7} and segmental⁷ dystonia, a good risk/benefit ratio has been demonstrated by two multicentre studies,^{6 7} with mean improvements in the dystonia motor score of 51%⁶ and 42% (double-blind)⁷ with little placebo effect.⁷ GPi-DBS has also been shown to be effective in segmental dystonia with cervical involvement,^{7 8 29 30–35} including in some large multicentre studies.^{8 24 29} The first prospective, single-blind, multicentre study assessing the efficacy and safety of bilateral GPi-DBS in cervical dystonia demonstrated a 55% improvement in dystonia on the Toronto Western Spasmodic Torticollis Rating Scale. The Toronto group defined a good response as a 50% or greater improvement. Pain, general health, physical functioning and depression scores also improved significantly.⁸ Stimulation with a smaller pulse width (71 µs)⁸ or a larger pulse width (219 µs)³⁶ gave similar results. The magnitude of improvement increased to 70% in a recent blinded study³⁷ with a median follow-up of 30 months. However, poor to no response was still rarely observed, although these patients differed in neither the clinical pattern of dystonia³⁶ nor the therapeutic position of the therapeutic contacts (adequate placement)³⁷ from those who did respond.

Although there is unpublished experience dating back almost 20 years, the longest published follow-up of patients undergoing GPi-DBS is 8 years²⁵ with an excellent outcome and sustained benefit in primary dystonia and up to 10 years (mean follow-up duration 6.2 years, range 3–10 years) in *DYT1*-positive patients.¹⁴ After 5 years, eight of these 26 patients required a second implantation because of worsening of dystonic symptoms. They were preoperatively indistinguishable from those who had a good and stable improvement after the primary procedure. However, the outcome was different in those who received an additional lead: four subsequently improved, although without reaching the previous optimal benefit, but the other four did not improve much, although neither did they relapse back to preoperative status.³⁸ Increasing the number of activated contacts and/or the voltage did not always provide additional improvement or control of all the signs in patients who respond well to therapy.

Other focal dystonia (cranial and upper limb)

Apart from cervical dystonia, the data regarding other forms of focal dystonia are limited to small series of mixed cases or individual reports and should be interpreted with caution, as some patients showed excellent improvement (up to 70%)^{38–40} and others had little or no benefit.⁴¹ In most cases, bilateral GPi stimulation was used. When staged implantation was performed, the best improvements were obtained when the second electrode was implanted.⁴² In patients who improve insufficiently after

treatment with botulinum toxin, DBS can be an acceptably effective therapy,⁴³ but the risk of the procedure has to be cautiously weighed against the benefit in these focal (and less severe) dystonias.

Cranial dystonia

Good results have been reported in blepharospasm and Meige syndrome (table 1).^{28 30 42 44–50} Blepharospasm improved in most patients, but the results on speech and swallowing were not so good.⁴¹ In a homogeneous series of patients with cranio-cervical and brachial segmental dystonia with oromandibular involvement,⁵¹ there was little effect on speech/swallowing scores at 6 months, but there was an improvement in function at 3 years follow-up (60%) even in patients who were almost anarthric before the procedure.⁵¹ This pattern of improvement as a function of site accords with results previously reported in generalised dystonia.

Beneficial effects could be obtained with low stimulation intensity (1.5 V, 90 µs, 130 Hz),⁴⁹ lower frequency (100 Hz)⁴¹ or cyclic stimulation mode, with the stimulator being programmed to turn off automatically during nighttime sleep.⁴⁰ Sustained long-term benefit was observed on follow-up of 49 ± 43.7 (mean ± SD) months.^{49 51 53}

In addition, surgery in cranial or craniocervical dystonia may give the opportunity to observe the effect of bilateral GPi stimulation on unaffected parts of the body: as the dystonia improves, motor function worsens in previously non-dystonic regions, with slowing of movement and difficulties with typing, handwriting or balance.⁴⁵

Upper limb dystonia

Severe writer’s cramp is rare, but patients with it have been successfully treated with unilateral DBS of the ventral oral (Vo) nucleus of the thalamus.^{60 61} This unusual target was chosen on the basis of encouraging results with unilateral thalamotomy in the Vo complex.^{62 63} In addition, bilateral stimulation of the ventral intermediate nucleus of the thalamus (Vim) has been successful in three cases of dystonic tremor.⁶⁴ However, in segmental or focal dystonia mainly involving the upper limbs or lower face, a decrease in the severity of dystonia is not meaningful without consistent improvement in hand function or speech. To date, this question has not been specifically addressed. The encouraging results with DBS in focal or segmental dystonia (except for severe cervical involvement) reported in case series have yet to be confirmed in larger studies. Beneficial effects have also been reported in axial dystonia,⁶⁵ limb dystonia^{63 66} and hip dystonia.⁶⁷

Predictive factors of outcome in primary dystonia

Age

From retrospective series, it appears that younger age at the time of surgery (<21 years old) and shorter duration of symptoms (<15 years) are the main predictive factors of good post-operative outcome at 1 and 3 years.^{25 68 69} Age at onset and severity of the disease have little or no significant influence.

Genetic status

DYT1-positive status was independently associated with significantly greater improvement after surgery,^{10 70} but this is still controversial.²⁴ Recent long-term follow-up data on *DYT1* mutation carriers suggest a possible secondary failure of DBS, challenging the assumption of *DYT1* mutations being a predictor of a beneficial clinical outcome. Worsening of symptomatology may be related to symptom spread (progressive disorder), with

Table 1 Blepharospasm and Meige syndrome

Reference	Age at surgery (years), mean (range)	Disease duration (years), mean (range)	Surgery	Stimulation parameters (R/L), mean (range)	% Improvement at lastF/U (range)	F/U
Limotai <i>et al</i> ⁴¹ n=6	56.3 (26–68)	11.3 (5–19)	GPI bilat	2.52 V (1.8–3.2)/2.75 V (1.5–3.5) 282 μ s (60–450)/265 μ s (60–450) 140 Hz (10–185)/127 Hz (10–185)	BFM (mov) 61.8% (16.6–100%) Blepharospasm improved in all patients No improvement in speech and swallowing	12 months
Reese <i>et al</i> ⁵² n=12	64.5 (57–72)	8.6 (4–18)	GPI bilat	3.8 V (2.4–5.0)/3.7 V (2.2–5.0) 143 μ s (60–210)/145 μ s (90–210) 170 Hz (130–235)	BFM (mov) FU1/FU2 45%/53% Subscores Eyes 38%/47% Mouth 50%/56% Speech 44%/64%	FU1 4.4 $\pm$ 1.5 months FU2 38 $\pm$ 21.7 months
Sako <i>et al</i> ⁵³ n=5	65 (54–72)	12 (7–18)	GPI bilat	2.6 V (1.0–3.9)/2.5 V (1.0–3.6) 392 μ s (210–450) 84 Hz (60–130)	BFM (mov) 84% (75–94%) BFM (dis) 89% (80–100%)	49 $\pm$ 43.7 months
Tai <i>et al</i> ⁴⁰ n=1	66	3	GPI bilat	2.2–3.2 V/2.2–3.2 V 450 μ s 60 Hz	BFM (mov) 75% *continuous mode until 24 months cycling mode 34–60 months	60 months
Ghang <i>et al</i> ⁵⁰ n=11	58.3 (45–70)	8.7 (1–20)	GPI bilat	3.4 V (2.6–5.0) 133.6 μ s (60–210) 143.1 Hz (60–185)	BFM (mov) at 12 months 74.5% Subscores Eyes 63.3% Mouth 80.9% Speech 68.4% Neck 87.9% BFM (mov) at 24 months (n=5) 85.5%	23.1 $\pm$ 6.4 months
Lyons <i>et al</i> ⁴⁷ n=3	73	N/A	GPI bilat	2.4 V/2.8 V 90 μ s 145 Hz	BFM (mov) 82%	54 months
	63	N/A	GPI bilat	3.6 V/3.0 V 120/60 μ s 60/90 Hz	50%	42 months
	56	N/A	GPI bilat	3.0 V/3.0 V 120 μ s 130 Hz	79%	48 months
Markaki <i>et al</i> ⁴⁸ n=1	49	7	GPI bilat	2.6 V/2.6 V 210 μ s 185 Hz	BFM (mov) 70% BFM (dis) 93%	6 months
Inoue <i>et al</i> ⁵⁴ n=1	61	18	GPI bilat	3.9 V/3.6 V 450 μ s 60 Hz	BFM (mov) 86% BFM (dis) 83%	10 years
Romito <i>et al</i> ⁴⁹ n=1	68	12	GPI bilat	1.3 V/1.3 V 90/90 μ s 130/130 Hz	BFM (mov) Subscores Eyes 100% Mouth 100% Speech 100% TWSTRS 93%	38 months
Blomstedt <i>et al</i> ⁵⁵ n=1	45	19	GPI bilat	5.2 V/4.9 V 120 μ s 145 Hz	BFM (mov) 71.5%	18 months
Ostrem <i>et al</i> ⁴⁵ n=6	62 (52–70)	8.2 (2–20)	GPI bilat	3.8 V (3.2–5.0)/3.65 V (2.9–5.0) 205 μ s (180–210)/190 μ s (90–210) 172 Hz (145–185)	BFM (mov) 72%Subscores Eyes 78.5% Mouth 73.3% Speech 48% TWSTRS 54%	6 months
Opherk <i>et al</i> ⁵⁶ n=1	65	N/A	GPI bilat	N/A	N/A	4 months
Houser and Waltz ⁴⁴ n=1	46	2	GPI bilat	3.8 V/2.6 V 210 μ s 160 Hz	BFM (mov) 75%	6 months

Continued

Table 1 Continued

Reference	Age at surgery (years), mean (range)	Disease duration (years), mean (range)	Surgery	Stimulation parameters (R/L), mean (range)	% Improvement at lastF/U (range)	F/U
Footte <i>et al</i> ⁴² n=1	47	5	GPI bilat	2.5 V/3.3 V 450 µs 185 Hz	UDRS 85% UDRS Eyes 57% Lower face 83%	15 months
Capelle <i>et al</i> ⁵⁷ n=1	60	5		4.3 V/4.3 V 210 µs 130 Hz	BFM (mov) Subscores Eyes 92% Mouth 75% Speech 33%	24 months
Vercueil <i>et al</i> ⁵⁸ n=1	59	15	GPI bilat	N/A	BFM (mov) 66%	6 months
Muta <i>et al</i> ⁵⁹ n=1	61	18	GPI bilat	3.6 V/3.6 V 500 µs 60 Hz	BFM (mov) 80%	N/A

BFM, Burke–Fahn–Marsden Dystonia rating scale; bilat, bilateral; dis, disability subscore; F/U, follow-up; GPI, internal globus pallidus; L, left; mov, movement subscore; n, number of individuals in each study; N/A, not available; pre-op, preoperative state; post-op, postoperative state; R, right; rest, rest subscore; TWSTRS, Toronto Western Spasmodic Torticollis rating scale.

an additional improvement after the second surgery (additional pair of electrodes).¹⁴

It is difficult to predict the influence of the *DYT6* genetic status, but the topographical specificity of patients with *THAP1* mutations (eg, severe cranial involvement) may be critical. Four patients with segmental or generalised dystonia and oromandibular and laryngeal involvement were treated with bilateral GPI stimulation, with moderate to good response on motor function but marginal benefit on speech,^{71 72} suggesting that the site of the dystonia (oromandibular) influences functional prognosis more than genetic status.

Cortical plasticity

Interindividual differences (endophenotype), such as the levels of cortical plasticity, may play a role in the beneficial effect of DBS.^{73 74}

In rare cases, and after several years of stimulation, sustained relief (>1 year) persisting after cessation of DBS has been observed in cervical dystonia⁶² and blepharospasm,⁷⁵ suggesting that DBS therapy may have the capacity to induce plastic change, which lessens or obviates the need for further treatment in susceptible patients.⁷⁵ In controlled studies with blind evaluation of the effects after the stimulator was switched off, the persistence of the beneficial effect was shorter and patients relapsed to their preoperative dystonia score after 30 h.⁷⁶

Orthopaedic complications

Fixed skeletal deformities⁷⁷ or cervical myelopathy^{78 79} may also be associated with a poorer outcome. Myelopathy should be sought from the third decade of life onwards, especially in patients with severe neck dystonia (BFM motor score for the neck >4). Gait disorders and falls, wasting of hand muscles, and bladder dysfunction were the best clinical predictors of cervical myelopathy.⁷⁸

Optimal placement of electrodes

Posteroventral GPI stimulation provides the best overall effect and is superior for the arm and trunk. Anterodorsal stimulation has equivalent efficacy for the leg.⁸⁰ External globus pallidus (GPe) stimulation may be harmful, with lack of improvement or even worsening of dystonia.⁸¹ This effect is even more

important in secondary dystonia such as dystonia-choreoathetosis cerebral palsy.⁸² Among the factors that influence the clinical outcome, the optimal placement of the electrodes within the pallidum seems the most critical, but is probably not the only one. Patients with optimally placed electrodes may still have a suboptimal response, and in this situation either additional electrodes³⁸ or an alternative target⁸³ should be considered. These authors also focused on brain imaging data and modelling the distribution of electrical current. Their predictive model suggested that (i) the greater the volume of the right GPI and (ii) the greater the volume of stimulated tissue within the left GPI, the greater the postoperative improvement.^{84 85}

Myoclonus-dystonia

Experience with fewer than 30 patients has been published to date (table 2). Myoclonus dystonia (M-D) is a rare form of movement disorder, with prominent action myoclonus and slight dystonia. By far the most common forms of dystonia in patients with M-D are cervical dystonia and writer's cramp. Although genetically heterogeneous, many cases are caused by point mutations or large deletions in the *ε*-sarcoglycan gene (*SGCE*). Genetically characterised patients received bilateral DBS targeting the GPI,^{86–91} the thalamus (Vim)^{92 93} or both targets.^{94 95} Stimulation of the Vim nucleus of the thalamus mainly improved the myoclonus⁹⁶ rather than the dystonia, whereas bilateral GPI stimulation improved both.^{91 95} Other patients with genetically undocumented myoclonic dystonia were also improved by pallidal stimulation.^{18 97 98} In the largest study⁹¹ of genetically proven M-D, it appeared that both myoclonus and dystonia were improved by 60–90% with bilateral GPI stimulation (based on blinded evaluation of the BFM Dystonia Rating Scale and Unified Myoclonus Rating Scale). Similar benefits were also reported even in patients in the 6th⁹³ or 7th decades of life,⁹¹ with concomitant improvement in quality of life and no significant adverse events. One report has highlighted the risk of psychiatric side effects in patients with a *SGCE* mutation, treated with GPI-DBS.⁸⁹

Taken together, these observations confirm the consistent motor improvement and acceptable safety of GPI stimulation in patients with M-D with *SGCE* mutation. This therapeutic option should therefore be considered for patients with severe

Table 2 Myoclonus-dystonia (*DYT11*)

Localisation	Reference	Age at surgery (years), median (range)	Duration of symptoms (years), mean (range)	Dystonia			Myoclonus			F/U
				Pre-op severity score, median (range)	Post-op severity score, median (range)	% Improvement (range)	Pre-op severity score, median (range)	Post-op severity score, median (range)	% Improvement (range)	
GPi	Azoulay-Zyss <i>et al</i> ⁹¹ n=5	42 (30–71)	26.4 (18–65)	BFM (mov) 30.0 (18.5–53.0) BFM (dis) 6 (5–13)	BFM (mov) 4.5 (3.5–16.0) BFM (dis) 2 (2–6)	85% (70–91) 66.6%	UMRS (rest and action) 76 (38–116)	UMRS (rest and action) 10 (6–31)	83% (73–93)	6–9 months
	Papuc <i>et al</i> ⁹⁰ n=1	31	27	BFM (mov)37	BFM (mov) 14	62%	N/A	N/A	N/A	6 months
	Kurtis <i>et al</i> ⁹³ n=1	63	61	BFM (mov) 38	BFM (mov) 22.5	41%	N/A	N/A	N/A	14 months
	Jog <i>et al</i> ⁸⁸ n=1	26	24	BFM (mov) 12	BFM (mov) 6	50%	UMRS (tot) 155	UMRS (tot) 52	66.5%	12 months
	Foncke <i>et al</i> ⁹⁶ n=2	39	36	BFM (mov) 22	BFM (mov) 9	59%	UMRS (rest/action) 42/38	UMRS (rest/action) 2/8	95%/79%	6 months
		18	11	BFM (mov) 10	BFM (mov) 4	60%	UMRS (rest/action) 18/30	UMRS (rest/action) 4/3	78%/90%	
	Cif <i>et al</i> ⁸⁷ n=1	8	7	BFM (mov) 9.5 BFM (dis) 9	BFM (mov) 1.5 BFM (dis) 1	84% 89%	UMRS (tot/rest/action) 69/16/20	UMRS (tot/rest/action) 13/1/2	81%/94%/90%	20 months
Vim	Kuncel <i>et al</i> ⁹² n=1	74	N/A	N/A	N/A	N/A	N/A	N/A	UMRS (action) 53% UMRS (funct) 14%	9 months
	Trottenberg <i>et al</i> ⁹⁶ n=1	60	54	N/A	N/A	N/A	Myoclonus scale* 116	Myoclonus scale* 23	80%	24 months

action, action subscore; BFM, Burke–Fahn–Marsden Dystonia Rating Scale; dis, disability subscore; ESRS, Extrapyrarnidal Symptom Rating Scale; F/U, follow-up; funct, functional subscore; GPi, internal globus pallidum; mov, movement subscore; n, number of individuals in each study; N/A, not available; pre-op, preoperative state; post-op, postoperative state; rest, rest subscore; tot, total subscore; Vim, ventral internal median nucleus of the thalamus; UMRs, Unified Myoclonus Rating Scale.

forms of this disorder (table 2). The place of pallidal stimulation in patients with myoclonic dystonia with undocumented genetic status remains to be determined.

Tardive dystonia (table 3)

Among the first patients with this condition to be treated with bilateral thalamus (Vim) and GPi stimulation was a 70-year-old woman in whom bilateral GPi-DBS gave a clear and subsequently stable improvement in her painful dystonic syndrome within hours, although thalamus DBS was ineffective (table 3).⁹⁹ Since then, single case reports and series have generally reported good results with GPi-DBS¹⁰⁰ with occasional failures.²⁶ In 2007, a multicentre study confirmed the observations of earlier cases series. In 10 consecutive patients, the Extrapyramidal Symptoms Rating Scale (ESRS) was improved by 61% after surgery (range 44–75%) in comparison with baseline. In the double-blind evaluation of the same patients, ESRS was 50% lower with stimulation than without stimulation. There were no changes in the patients' psychiatric status.¹⁰¹ In another report, a reduction in movement disorders by 80% has been observed, both on the motor and disability scores of the BFM and abnormal involuntary movement scales in addition to an improvement in quality of life.¹⁰² The extrapyramidal symptoms and dystonia improved rapidly after the DBS was switched on (sometimes within a few days).^{100 103 104} The motor benefit has been observed to be sustained^{103 105} on mean follow-up of 41 (range 18–80) months,¹⁰² up to a maximum of 8 years.¹⁰⁶

The overall risk/benefit ratio of DBS in tardive dystonia is favourable, with no serious side effects being reported across the studies. In addition, affect also improved significantly, while cognitive functions remained unchanged compared with presurgical status on long-term follow-up.^{102 105 107}

GPi-DBS and cognitive functions/quality of life

There is little impact on cognitive function and behaviour with bilateral GPi-DBS in primary dystonia (generalised or segmental/cervical dystonia).^{7 33 114–116} Some improvements have been reported, but this may be related to the reduction in dose of anticholinergic drugs, made possible by successful DBS treatment. There are some biases in these studies, as the patients were highly selected, with, at inclusion, normal cognitive performances and no mood disorders (patients with depression were excluded) at baseline. A list of preoperative tests on a routine basis is recommended,¹¹⁷ including the Wechsler Adult Intelligence Scale (WAIS) III in adults and Wechsler Intelligence Scale for Children (WISC) in children. In patients with primary dystonia, depression and anxiety scores remain stable.

Quality of life, assessed by the Short Form (36) Health Survey (SF36), shows improvement both in mental and physical categories.^{115 117 118}

Dystonia with poor or less predictable favourable outcome

Status dystonicus

Status dystonicus is an acute and persistent combination of generalised dystonia and chorea. It represents an emergency and may occur in primary dystonia (including *DYT1*) or any kind of secondary dystonia including cerebral palsy, patients with *PANK2* mutations, Wilson's disease and Batten disease.¹¹⁹ Common triggers for status dystonicus include general anaesthesia, the administration of metoclopramide, or infection and fever. The single cases and heterogeneous series reported^{116 120} suggest that GPi-DBS should be considered as a potential treatment in these life-threatening events (table 4), with

improvement in pain and dystonia,^{120–123} although there may be a publication bias for cases with positive outcomes.

Secondary dystonia

We have focused on hereditary degenerative and metabolic disorders (table 5). The issue of DBS for dystonia secondary to brain injury is strongly debated.¹⁰⁸ Patients with secondary dystonia have complex movement disorders with a combination of hyperkinetic and akinetic-rigid dystonia. In addition, the targeted structure (DBS target) often has lesions, and the pathological process may be progressive (as in inherited metabolic disorders). Standardised assessment of global motor and functional outcomes (beyond the reduction of dystonia) is difficult because of the lack of adequate evaluation tools. However, the recent literature contains some reports of the benefit of this treatment in such patients.

In a pioneering controlled study of 13 patients with dystonia-choreoathetosis cerebral palsy due to neonatal hypoxic encephalopathy, GPi-DBS provoked a 24% decrease in the mean BFM motor score 12 months after surgery.⁸² Four patients improved by 39–55%; four did not respond (improvement <20%). Disability, mental health and body pain-related quality of life improved slightly. Several other case reports also suggested that GPi-DBS could offer a therapeutic alternative for dystonia due to various focal brain lesions and inherited metabolic or genetic disorders. There is evidence to suggest that GPi-DBS may be effective in patients with *PANK2* mutations (average motor improvement of 30%, although with marked variability).^{129 135 134 137} Anecdotal reports also indicate that GPi-DBS could be useful in patients with dystonia secondary to GM1 gangliosidosis,¹⁵⁰ mitochondrial disorder with striatal necrosis,¹⁵¹ Lesch-Nyhan disease^{138 145 144 152} and X-linked parkinsonism.¹⁵³ As the literature is sparse, the selection of patients for DBS in secondary dystonia is highly challenging, and cases should be discussed by a multidisciplinary team on an individual basis. Our experience and literature review suggest that three aspects must be considered: (i) the clinical picture (GPi stimulation may be more effective on hyperkinetic movement disorders); (ii) the distribution of the brain lesions; and (iii) careful evaluation of the functional aim and the patient's expectations.

SAFETY: LONG-TERM SIDE EFFECTS

In addition to well-established hardware-related (such as infection, haemorrhage, leads or extension fractures) and stimulation-related (dysarthria) side effects, some unusual deleterious effects have been reported in a few dystonic patients chronically treated with GPi-DBS. Acquired stuttering was described in two patients under conditions that optimally suppressed dystonic symptoms, with marked disability in one case.¹⁵⁴ Parkinsonism was also reported in patients with cranial-cervical dystonia.^{155 156} Hypokinetic gait disorder and freezing of gait¹⁵⁷ in dystonia are not related to electrode misplacement. A shuffling gait and difficulties with gait initiation may be triggered by voltage increases, while modification of other variables such as pulse width or frequency does not seem to help much. A compromise between optimal stimulation for dystonia and undesirable effects such as freezing of gait must be obtained.

Mood disorders should be carefully assessed, given reports of postoperative suicide.^{158 159} Patients with mild to moderate depression, including patients with history of depression (tardive dystonia) appear to do well after the operation. However, there are few data on patients with severe mood disorders (active depression is currently an exclusion criterion for surgery). Screening and management strategies before and after surgery are available for patients identified as having a major psychiatric illness.¹¹⁷

Table 3 Tardive dystonia

Reference	Age at surgery (years), mean (range)	Disease duration (years), mean (range)	Stimulation parameters R/L	Pre-op severity score, mean (range)	Post-op severity score, mean (range)	% Improvement at last F/U	F/U
Chang <i>et al</i> ¹⁰⁶ n=5	57.8 (28–59)	10.6 (6–20)	3.14±0.5 V/2.9±0.45 V 204±13.4/198±16.4 μ s 130±56 Hz	BFM (mov) 47.9 BFM (dis) 11.8	BFM (mov) 14.5 BFM (dis) 6.2	70.9±12% 47.9±18%	34 months (15–76) median (range)
Capelle <i>et al</i> ¹⁰⁷ n=4	45	4	gr parameters 4.5 V (3.0–6.5) 90–210 μ s 130–160 Hz	BFM (mov) 65 BFM (dis) 8	BFM (mov) 5.5 BFM (dis) 1	91% 88%	27 months
	76	11		55 6	16 3	70% 50%	30 months
	65	7		18 1	2 0	88% 100%	16 months
	48	5		33 8	4.5 4	87% 50%	36 months
Gruber <i>et al</i> ¹⁰² n=9	63.2 (38–76)	5.3 (2–11)	3.0±1.0 V/2.8±0.6 V 83.3±13.2 μ s 154±25.1 Hz	– – –	– – –	BFM (mov) 83±12.2% BFM (dis) 67.7±28% AIMS 78.7±19.9%	41 months (18–80) mean (range)
Katsakiori <i>et al</i> ¹⁰⁸ n=1	40	3	N/A	BFM (mov) 35 BFM (dis) 19	BFM (mov) 2 BFM (dis) 3	94% 84%	12 months
Kefalopoulou <i>et al</i> ¹⁰⁹ n=1	42	3	2.5–3.6 V 250–400 μ s 185 Hz	BFM (mov) 52 AIMS 30	BFM (mov) 4.5 AIMS 7	91% 77%	6 months
Magarinos-Ascone <i>et al</i> ¹¹⁰ n=1	59	4	N/A	BFM (mov) 46 BFM (dis) 16	BFM (mov) 24 BFM (dis) 9	48% 44%	12 months
Sako <i>et al</i> ¹⁰⁵ n=6	44.5 (31–64)	3.1 (0.5–6)	2.2±0.9 V 450 μ s 119±28 Hz		– –	BFM (mov) 86±14% BFM (dis) 80±12%	21 months
Pretto <i>et al</i> ¹¹¹ n=1	72	N/A	4.0 V 90 μ s 185 Hz		BFM (mov) 1	90%	3 months

Continued

Table 3 Continued

Reference	Age at surgery (years), mean (range)	Disease duration (years), mean (range)	Stimulation parameters R/L	Pre-op severity score, mean (range)	Post-op severity score, mean (range)	% Improvement at last F/U	F/U
Cohen <i>et al</i> ¹⁰⁴ n=2	44	4	4 V 90 μ s 130 Hz		BFM (mov) 3 BFM (dis) 0	86% 100%	13 months
	50	4	4 V 120 μ s 130 Hz	31.5 19	11.5 9	64% 53%	7 months
Damier <i>et al</i> ¹¹² n=10	45.1 (26–69)	4.5 (1–10)	3.5 $\pm$ 0.2 V 150 μ s 130 Hz	– –	– –	ESRS 61% (44–75) AIMS 56% (33–69)	6 months
Starr <i>et al</i> ²⁷ n=4	36	7	N/A	BFM (mov) 11	BFM (mov) 0	100%	26 months
	47	4	N/A	38	7.5	80%	27 months
	59	20	N/A	57	53.5	6%	17 months
	36	10	N/A	80	37.5	53%	9 months
Zhang <i>et al</i> ¹¹³ n=1	28	3	STN bilat 1.5 V/3.0 V 90 μ s 185 Hz	BFM (mov) 98.5 UDRS 94	BFM (mov) 8 UDRS 7.5	92% 92%	3 months
Franzini <i>et al</i> ¹⁰⁰ n=2	33	5	1 V 90 μ s 130 Hz	BFM (mov) 36	BFM (mov) 5	86%	12 months
	30	3	1 V 90 μ s 130 Hz	70	8	89%	13 months
Trottenberg <i>et al</i> ¹⁰³ n=5	56.2 (30–70)	N/A	2.7 $\pm$ 0.8 V 111 $\pm$ 57 μ s 144 $\pm$ 22 Hz	BFM (mov) 32 BFM (dis) 8	– –	87% 96%	6 months
Krause <i>et al</i> ²⁶ n=2	53.7	5.7	N/A	BFM (mov) 62	BFM (mov) 63.5	–2%	30 months
	47.6	22.6	N/A	76	77	–1%	42 months
Eltahawy <i>et al</i> ²⁰ n=1	53	4	2.6 V 210 μ s 40 Hz	BFM (mov) 52	BFM (mov) 21	60%	18 months
Yianni <i>et al</i> ¹⁸ n=1	40	5	N/A	AIMS 24	AIMS 14	42%	12 months

AIMS, Abnormal Involuntary Movement Scale; action, action subscore; BFM, Burke–Fahn–Marsden Dystonia Rating Scale; bilat, bilateral; dis, disability subscore; ESRS, Extraparalysmal Symptom Rating Scale; F/U, follow-up; funct, functional subscore; GPi, internal globus pallidum; L, left; mov, movement subscore; n, number of individual in each study; N/A, not available; NST, ; pre-op, preoperative state; post-op, postoperative state; R, right; rest, rest subscore; tot, total subscore; UMRS, Unified Myoclonus Rating Scale; STN, subthalamic nucleus.

Table 4 Status dystonicus

Reference	Age (years)/sex	Aetiology	Precipitating factor	Surgery	Delay in improvement	Outcome	F/U	Complications
Walcott <i>et al</i> ¹²³ n=3	14/M 9/F 9/F	Kernicterus perinatal/CP Generalised dystonia CP	Spinal surgery Unknown Upper respiratory illness	GPI bilat GPI bilat GPI bilat	Few days Few weeks Few weeks	+ + (R side) +	12 months 3 months 3 months	L lower contact partially working Infection (explantation R) None
Kovacs <i>et al</i> ¹²⁴ n=1	18/M	Tardive dystonia	No apparent	GPI bilat	Few days	BFM pre-op (mov/dis) 108/28 BFM post-op 2 weeks 42/18 BFM post-op 1 year 3.5/1	12 months	None
Grandas <i>et al</i> ¹²⁵ n=1	19/M	NBIA (PANK2)	No apparent	GPI bilat	Few days	BFM pre-op (mov/dis) 96/29 BFM post-op 9 months 10/4	9 months	None
Apetauerova <i>et al</i> ¹¹⁶ n=2	16/M 26/M	CP CP	Surgery/metoclopramide surgery	GPI bilat GPI bilat	Few hours Few days	+ (Returned to baseline functional status) + (Returned to baseline functional status)	30 months 34 months	None None
Jech <i>et al</i> ¹²⁶ n=1	12/M	Generalised dystonia	No apparent	GPI bilat	Few weeks	BFM pre-op (mov) 41 BFM post-op 2 months 5 BFM post-op 15 months 3	15 months	None
Elkay <i>et al</i> ¹¹⁹ n=1	19/F	Batten's disease	No apparent	Pallidotomy GPI bilat	Few days	BFM (mov) off stim 100 BFM on stim 62	7 months	None
Mariotti <i>et al</i> ¹²² n=1	15/M	NBIA (PANK2)	Recurrent infection (upper respiratory illness/pneumonia)	GPI bilat*	N/A	+ No recurrence of status dystonicus	12 months	None
Teive <i>et al</i> ¹²¹ n=1	57/M	Generalised dystonia	Stress	GPI bilat	N/A	++	N/A	Mild L hemiparesis
Zorzi <i>et al</i> ²¹ n=3	8.2/M 14.2/M 10.6/M	Generalised dystonia Encephalopathy unknown origin Generalised dystonia	Upper respiratory illness No apparent No apparent	GPI bilat GPI bilat GPI bilat	Few months Few days Few days	BFM pre-op (mov/dis) 91/20 BFM post-op at last F/U 83/19 BFM pre-op (mov/dis) 43/12 BFM post-op at last F/U 43/12 BFM pre-op (mov/dis) 79.5/19 BFM post-op at last F/U 63/10	15 months 15 months 19 months	Unpredictable switching off None† Unpredictable switching off
Angelini <i>et al</i> ¹²⁷ n=1	13/M	Unknown TH deficiency?	N/A	GPI bilat	Few days	+	7 months	None

*DBS performed some months after the status dystonicus and not in an emergency situation.

†Reimplantation procedure after an infection 2 years ago.

action, action subscore; BFM, Burke–Fahn–Marsden Dystonia Rating Scale; bilat, bilateral; CP, cerebral palsy; DBS, deep brain stimulation; dis, disability subscore; F, female; F/U, follow-up; funct, functional subscore; GPI, internal globus pallidum; L, left; M, male; mov, movement subscore; n, number of individuals in each study; N/A, not available; pre-op, preoperative state; post-op, postoperative state; R, right; stim, stimulation; TH, tyrosine hydroxylase; = no improvement; + = good outcome; ++ = excellent outcome (according to outcome described by the authors).

Table 5 Secondary dystonia: neurodegenerative and metabolic disorders

Subtype	Reference	Age at surgery (years), mean (range)	Disease duration (years), mean (range)	Pre-op severity score, mean (range)	Post-op severity score, mean (range)	% Improvement	F/U
Hereditary degenerative							
NBIA	Umemura <i>et al</i> ¹²⁸	36	28	BFM (mov)	BFM (mov)	80%	12 months
	n=1	21 (10–39)	10 (2–22)	112	22.5	74.6% (46–	20.6 months
	Castelnau <i>et al</i> ¹²⁹	8	2	BFM (mov)	BFM (mov)	91.5%)	(6–42)
	n=6	43	13	75.1 (45.5–102)	20.1 (5.5–46.5)	53% (21–82)	Death
	Sharma <i>et al</i> ¹³⁰	13	7	BFM (dis)	BFM (dis)	None	at 3 months
	n=1	17	8	20 (7–30)	9.7 (3–23)		12 months
	Starr <i>et al</i> ²⁷	16	10	N/A	N/A	80%	5 years
	n=1	11	8.5	BFM (mov)	BFM (mov)	70%	N/A
	Krause <i>et al</i> ¹³¹	18 (6–36)	10.2 (3–28)	30	6	24%	24 months
	n=1	17.5	8.5	BFM (mov)	BFM (mov) at	23%	Infection
	Shields <i>et al</i> ¹³²	N/A	N/A	92	1 year	31%	at 3 months
	n=1	N/A	N/A	BFM (mov)	30	66.7%	F/U1
	Isaac <i>et al</i> ¹³³	N/A	N/A	86	BFM (mov) at	FU1	2–6 months
	n=1	N/A	N/A	BFM (mov)	5 years	28.5%	F/U2
	Mikati <i>et al</i> ¹³⁴			105	70	FU2	9–15 months
	n=1			Barry–Albright	BFM (mov)	25.7%	
	Timmermann			Dystonia Scale	66	81%	4.5 years
	<i>et al</i> ¹³⁵			24	BFM (mov)	71%	6 months
	n=24*			71.2 (21–112)	72	51%	12 months
	Adamovicova			77.5	Barry–Albright	28%	12 months
	<i>et al</i> ¹³⁶			BFM (mov)	Dystonia Scale	22%	12 months
	n=1			96	8	N/A	
	Lim <i>et al</i> ¹³⁷			79.5	N/A	0%	
	n=4			44.5	15	9.5%	
				46	22.5	0%	
					38	0%	
					BFM (mov) at	46%	
					3 months	15%	
					69	–22%	
					BFM (mov) at 6 m	5.4%	
					74.5	15%	
					BFM (mov) at		
					12 months		
					N/A		
					79.5		
					72		
					80		
					44.5		
					24		
					38		
					56		
					43.5		
					39		
Lesch–Nyhan	Cif <i>et al</i> ¹³⁸	16	15	BFM (mov)	BFM (mov)	41%	28 months
	n=1	8	7	78.5	46.5	BFM (mov)	30 months
	Deon <i>et al</i> ¹³⁹			N/A	N/A	50%	
	n=1						
Cockayne syndrome	Hamasaki <i>et al</i> ¹⁴⁰	52	22	BFM (mov)	BFM (mov)	56.7%	5 months
	n=1			45	19.5		
Dystonia deafness	Havrankova <i>et al</i> ¹⁴¹	29	5	BFM (mov)	BFM (mov)	75%	10 months
	n=1			53	13		
Lubag X-linked dystonia parkinsonism	Evidente <i>et al</i> ¹⁴²	45	14	BFM (mov)	BFM (mov)	76.3%	12 months
	n=1	34		UPDRS	UPDRS	75.8%	12 months
		66	1	40	9.5	80.6%	12 months
	Martinez-Torres	39	9	33	8	78.4%	12 months
	<i>et al</i> ¹⁴³	32	3	77.5	15	10.4%	12 months
	n=1			37	8	67.9%	
	Oyama <i>et al</i> ¹⁴⁴		2	48	43	80.4%	
	n=1			14	4.5	5%	
	Wadia <i>et al</i> ¹⁴⁵			87	17	88.3%	
	n=1			40	38	57.9%	
	Aguilar <i>et al</i> ¹⁴⁶			40.5	4.75		
	n=1			9.5	4		
Rapid-onset dystonia parkinsonism	Deutschlander	21	2	BFM (mov)	BFM (mov)	0%	27 months
	<i>et al</i> ¹⁴⁷	24	12	50	50	26%	12 months
	n=1			BFM (mov)	BFM (mov)	3.2%	
				55.5	41		

Continued

Table 5 Continued

Subtype	Reference	Age at surgery (years), mean (range)	Disease duration (years), mean (range)	Pre-op severity score, mean (range)	Post-op severity score, mean (range)	% Improvement	F/U
Metabolic diseases	Kamm <i>et al</i> ¹⁴⁸ n=1			UPDRS 93	UPDRS 90		
Homocystinuria	Aydin <i>et al</i> ¹⁴⁹ n=1	23	8	BFM (mov) 60	BFM (mov) 5.5	91%	7 months
GM1 gangliosidosis	Roze <i>et al</i> ¹⁵⁰ n=1	24	8	BFM (mov) 70 UPDRS 37	BFM (mov) 56 UPDRS 32	20% 14%	12 months

*Four patients already cited by Umemura *et al*,¹²⁸ Krause *et al*,¹³¹ Shields *et al*.¹³²

BFM, Burke–Fahn–Marsden Dystonia Rating Scale; dis, disability subscore; F/U, follow-up; mov, movement subscore; n, number of individuals in each study; N/A, not available; NBIA, neurodegeneration with brain iron accumulation; pre-op, preoperative state; post-op, postoperative state; UPDRS, Unified Parkinson Disease Rating Scale.

CURRENT PRACTICE AND LEADS FOR THE FUTURE

Beside the checklist of exclusion criteria,¹⁶⁰ the preoperative assessment aims to characterise the severity of dystonia and to evaluate the mood, cognition and quality of life. Detailed description of preoperative selection,¹⁶⁰ evaluation^{161–117} and postoperative management¹⁶² is beyond the scope of this review and is fully detailed in the *Movement Disorders Journal* supplement (2011) dedicated to the management of DBS in dystonia.

Although the decision may appear relatively easy and straightforward for primary dystonia, myoclonus-dystonia and tardive dystonia, reliable tools to help accurate prediction of postoperative beneficial effects and the time course of improvement are still lacking.

Several authors have made detailed recommendations about DBS in the treatment of adult dystonia,^{10–15} but paediatric guidelines are lacking, mainly because of the absence of controlled studies in this age group. Management of DBS in childhood dystonia differs in several aspects from that of DBS in dystonic adults: (i) childhood dystonia is more often secondary than primary; (ii) mixed motor disorders are common (eg, dystonia associated with spasticity); (iii) the course of dystonia may be influenced by ongoing brain maturation and by the plasticity of the brain; (iv) the therapeutic strategy must be discussed with both the patient and his/her parents; and (vi) the child's education must be taken into account. In addition, the overall incidence of wound breakdown and hardware infection requiring device removal seems to be higher in children than in adults.^{16–163}

As in adults, there is no reliable way of predicting outcome for a given subject. Although not specifically studied in the paediatric population, pallidal DBS is also a relevant option in children with severe medically refractory myoclonus-dystonia syndrome.⁸⁷ However, the possibility of spontaneous improvement in dystonia during childhood¹⁶⁴ in this setting should be considered during discussion of the therapeutic strategy, especially when DBS is being considered.

In secondary dystonia, the main challenge is to determine which evaluation tool to use to capture any functional benefit in DBS. The BFM dystonia scale, the gold standard scale used in therapeutic trials for dystonia, may fail to measure subtle but relevant clinical effects of DBS on the child's participation in everyday activities. In this context, the goals of DBS may be more related to improving comfort and quality of life rather than motor function per se, even in the absence of significant change in BFM severity subscore.¹⁶⁵

CONCLUSION

GPI-DBS has long-term efficacy and safety in severe primary generalised and cervical dystonia but late unusual complications such as akinesia or freezing of gait may rarely occur. Tardive dystonia or myoclonus dystonia may also represent good indications. Clinical predictive factors of favourable outcome for GPI-DBS in dystonia have emerged in the past few years, but there is a need for more reliable markers that will help to accurately select dystonic patients who will benefit from DBS. Alternative targets have been recently proposed, with variable beneficial effects of subthalamic stimulation in cervical dystonia,¹⁶⁶ but with a risk of adverse effects such as weight gain or transient dyskinesia.

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