Deep brain stimulation versus pallidotomy for status dystonicus: a single-center case series

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OBJECTIVE First-line pharmacological therapies have shown limited efficacy in status dystonicus (SD), while surgery is increasingly reported as remediable in refractory cases. In this context, there is no evidence regarding which neurosurgical approach is the safest and most effective. The aim of this study was to assess the clinical outcomes and surgery-related complications of globus pallidus internus deep brain stimulation (GPi DBS) and pallidotomy for the treatment of drug-resistant SD.

METHODS The authors reviewed the records of patients with drug-resistant SD who had undergone GPi DBS or pallidotomy at their institution between 2003 and 2017. The severity of the dystonia was evaluated using the Barry-Albright Dystonia (BAD) Scale. Surgical procedures were performed bilaterally in all cases.

RESULTS Fourteen patients were eligible for inclusion in the study. After surgery, the mean follow-up was 40.6 ± 30 months. DBS ended the dystonic storm in 87.5% of cases (7/8), while pallidotomy had a success rate of 83.3% (5/6). No significant differences were observed between the two techniques in terms of failure rates (risk difference DBS vs pallidotomy -0.03 , 95% CI -0.36 to 0.30), SD mean resolution time (DBS 34.8 ± 19 days, pallidotomy 21.8 ± 20.2 days, $p > 0.05$), or BAD scores at each postoperative follow-up ($p > 0.05$). The long-term hardware complication rate after DBS was 37.5%, whereas no surgery-related complications were noted following pallidotomy.

CONCLUSIONS The study data suggest that DBS and pallidotomy are equally safe and effective therapies for drug-resistant SD. The choice between the two techniques should be tailored on a case-by-case basis, depending on factors such as the etiology and evolution pattern of the underlying dystonia and the clinical conditions at the moment of SD onset. Given the limitation of the low statistical power of this study, further multicentric investigations are needed to confirm its findings.

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KEYWORDS deep brain stimulation; DBS; pallidotomy; status dystonicus; dystonia; dystonic storm; ablative surgery; functional neurosurgery

STATUS dystonicus (SD) is a rare but life-threatening movement disorder emergency characterized by severe episodes of generalized or focal dystonia potentially accompanied by other hyperkinetic movements that have necessitated urgent hospitalization, regardless of the patient's neurological condition at baseline.^{24,26,29} Also known as “dystonic storm,” SD is frequently reported in children and can be triggered by several precipitating factors, such as infections, drug withdrawal, and surgical

procedures.^{1,25} Early recognition and intervention are paramount in cases of SD, as its persistence often leads to serious sequelae, such as rhabdomyolysis and respiratory failure, with consequent high mortality rates (10%–15%).^{1,27}

There is still no consensus on the optimal strategy for treating SD. Antidystonic drugs and profound sedation usually represent the first therapeutic options. Unfortunately, their efficacy is limited and surgical alternatives are needed in the majority of cases.¹⁵ An increasing number

ABBREVIATIONS AC-PC = anterior commissure–posterior commissure; BAD = Barry-Albright Dystonia; DBS = deep brain stimulation; GPi = globus pallidus internus; ITB = intrathecal baclofen; MNI = Montreal Neurological Institute; SD = status dystonicus; SP = staged pallidotomy.

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of clinical studies have shown the effectiveness of deep brain stimulation (DBS) of the globus pallidus internus (GPi) in cases of drug-resistant SD.^{5,6,23,32,37,42,44,45} However, one shortcoming of DBS is the nonnegligible risk of hardware-related complications in the pediatric dystonia population.²⁸ In addition, several reports have described the onset of severe or fatal SD as a consequence of a DBS depleted battery or lead dislocation.^{34–36} Also, DBS may not be effective in resolving SD. In a recent study by Nerrant et al., 2 patients died as a direct consequence of refractory SD, despite attempts at subsequent rescue DBS therapy.³² In this context, ablative procedures such as pallidotomy, which does not require any hardware implantation, are likely to be of benefit. However, their effectiveness for SD has been reported in only sporadic case reports and small case series.^{8,9,14,17,28,33}

The primary aim of the present study was to compare the clinical outcomes and surgery-related complication rates of pallidotomy and GPi DBS for the treatment of SD in a single-center cohort. Potential correlations among SD characteristics, type of neurosurgical treatment, and outcomes were then analyzed and discussed.

Methods

Study Design and Data Collection

The records of patients with drug-resistant SD who had undergone GPi DBS or pallidotomy at our institution between 2003 and 2017 were reviewed. All the surgical procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments. Patients or their relatives provided written informed consent in all cases.

Inclusion criteria for drug-resistant SD included patients of any age with abrupt exacerbation of the baseline dystonic phenomenology, unresponsiveness to at least 2 antidystonic medications, urgent intensive care unit (ICU) admission with profound sedation, and at least one of the Manji diagnostic criteria (Table 1).²⁶ Discharge from the ICU was chosen as the event indicative of the end of the dystonic storm. The following data were collected: patient demographics, baseline dystonia characteristics (age, sex, dystonia etiology, age at onset of dystonia, disease duration before SD, trigger factors), and hospital course (medications, time between SD onset and surgery, type of surgery, SD resolution or persistence, complications). Dystonia severity was evaluated according to the Barry-Albright Dystonia (BAD) Scale at the last available visit before onset of the dystonic storm (baseline BAD), during the storm (SD BAD), 1 month after surgery (postoperative BAD), and at the last available follow-up (last BAD).³⁹ Clinical outcomes at 1 month after surgery were categorized according to a modified Ben-Haim scale (Table 1).⁶ During telephone interviews conducted in June 2018, all caregivers rated their experience with long-term caregiving and patient comfort levels after surgery by using a subjective rating scale (Table 1).

Surgical Procedures

GPi DBS

GPi DBS was usually considered the first surgical

TABLE 1. Various scales used in the study

Manji diagnostic criteria
Bulbar weakness compromising upper airway patency
Physical exhaustion & pain
Metabolic imbalances such as myoglobinuria
Renal or respiratory failure
Modified Ben-Haim scale
1, death
2, SD resolution w/ deterioration from baseline dystonia (BAD increase >25%)
3, SD resolution but w/ unchanged baseline dystonia (BAD variation btwn ±25%)
4, SD resolution w/ slight improvement of baseline dystonia (BAD reduction >25% but <50%)
5, SD resolution w/ great improvement of baseline dystonia (BAD reduction ≥50%)
Subjective caregiver benefit scale
–1, worse than expected
0, no benefit
1, minimal benefit
2, good benefit, as expected
3, excellent benefit, more than expected

option in patients with a good nutritional state and progressive baseline dystonia course. Surgery was always performed under general anesthesia, bilaterally, and under stereotactic conditions with the Leksell (Elekta Inc.) or Maranello (Eidos22) frame. Our routine surgical procedure has been extensively discussed elsewhere.¹⁶ GPi coordinates related to the anterior commissure–posterior commissure (AC-PC) midpoint were set at X (±19), Y (+2), and Z (–6) in all cases.

Conventional and Staged Pallidotomy

Conventional pallidotomy was routinely performed under general anesthesia and in stereotactic conditions for the following indications: 1) previous DBS failure, 2) patients with a high risk for DBS hardware-related complications (e.g., those having a low body weight, severe malnutrition, or poor skin condition), and 3) patients who were not usually considered good DBS candidates at our institution because of poor expected responsiveness to stimulation (severe acquired dystonia characterized by a long, static disease course and by the absence of a period of normal development). Based on previous studies of pallidotomies, ablation was performed in the midportion of the GPi, which is still part of the posteroventral GPi.^{10,28} This targeting technique, in which the target was always defined using direct visualization on preoperative images given the frequent anatomy distortion in these patients, allows for immediate benefit for dystonic symptoms, without preventing patients from receiving further gain from subsequent DBS of the most posterior part of the GPi.²⁸

The radiofrequency monopolar lesions were always created bilaterally at the target, 2 mm above it, and 2 mm below it, through a CSK-TC20 electrode (Cosman Medical; 4-mm exposed uninsulated tip, 1 mm in diam-

eter) with a 60-second train of 40 V through the radiofrequency generator, reaching a temperature of 70°C. The heat generated during the lesioning process was usually monitored, with a thermistor recording the temperature at the probe tip. Microrecording and macrostimulation were performed under electromyography monitoring to exclude involvement of pyramidal fibers of the internal capsule by the lesioning.

More recently, bilateral staged pallidotomy (SP) has been gradually introduced at our institution. Quadripolar DBS leads (3389, Medtronic) are used to generate the ablation by connecting their extracranial termination to a radiofrequency generator (RFG-1A, Cosman Medical).^{4,18} SP can be used *de novo*, as a salvage treatment after previous DBS failure, or prior to lead removal because of DBS hardware infection. Its main advantages include the possibility of checking the definitive electrode location prior to lesioning and monitoring ablation evolution over time.¹⁸ The lesion is usually created in a bipolar fashion between lead central contacts 2 days after surgery with a 40-second train of 40 V. If needed, the ablation can be easily repeated in the following days. Once the pallidotomy effect is achieved, leads can be left in place (should the patient need DBS in the future) or removed.

Postoperative Lead and Lesion Localization

In the case of DBS or SP, the postoperative CT scan was merged with the preoperative MR image (Framelink, Medtronic) to assess the definitive lead location in the AC-PC space. Final coordinates were identified as the center of the beam-hardening artifact representing the deepest contact (contact 0). The position in the Montreal Neurological Institute (MNI) space of all DBS leads was also detected and reconstructed three-dimensionally by using the Lead-DBS MATLAB toolbox.²⁰

In cases of conventional pallidotomy, lesion location was evaluated in the AC-PC space by merging the postoperative MR image (usually obtained within 1 week after surgery) with the preoperative volumetric CT scan. The center of the lesion was identified in the axial slice in which the lesion had the largest diameter.

Statistical Analysis

Descriptive statistics were provided as percentages for dichotomous data and the mean $\pm$ standard deviation for continuous data. Preoperative differences between patients who had undergone DBS and those who had been treated with pallidotomy were evaluated using unpaired t-tests. Differences between SD BAD and postoperative BAD scores were assessed using paired t-tests. Repeated measures ANOVA was used to compare postoperative BAD scores between DBS and pallidotomy groups. Pearson correlation coefficients were used to assess significant associations between the effect of surgery (in terms of the difference between SD BAD score and postoperative BAD score) and baseline dystonia duration or time spent in SD before the final surgery. Statistical analyses were performed using Stata statistical software (release 15, 2017, StataCorp LLC). Statistical significance was set at $p \leq 0.05$.

Results

Patient Demographics and Baseline Characteristics

Demographic data and baseline dystonia characteristics are shown in Table 2. Fourteen patients fulfilled the inclusion criteria for the study. The cohort included 12 pediatric and 2 adult patients. Three patients (21.4%) experienced a prior SD episode, which had been successfully managed with antidystonic drugs. Dystonia etiology was identified in all but 1 case.

All patients had severe generalized dystonia and were on oral antidystonic treatment prior to the onset of SD; 4 of them also had an intrathecal baclofen (ITB) pump. The mean baseline BAD score before the onset of SD was 21.8 ± 3.6 points.

Characteristics of the Dystonic Storms

The mean age at SD onset was 11.8 ± 5 years. The temporal course of SD onset ranged from days to weeks in 85.7% (12/14) of patients, whereas slow worsening of dystonia over a few months was documented in 2 subjects, one affected by a GNAO1 encephalopathy and one suffering from a dyskinetic cerebral palsy (2/14 [14.3%]). Triggering factors were identified in 50% (7/14) of cases (Table 2). Among those patients with an ITB pump, 2 developed SD as a consequence of ITB-related adverse events (1 malfunction and 1 infection), while ITB malfunction was ruled out in the remaining cases.

The mean SD duration was 74.6 ± 55 days. The mean SD BAD score was 31.2 ± 0.8 points. No significant preoperative differences were found between patients who underwent DBS and those who were treated with pallidotomy in terms of age at dystonia onset, age at SD onset, duration of dystonia, time between SD onset and surgery, baseline BAD scores, and SD BAD scores (all $p > 0.05$).

Clinical Outcomes

The mean dystonia duration before surgery was 7.8 ± 4.1 years, while the mean time from SD onset to surgery was 30.3 ± 20.3 days. After surgery, the total BAD scores were significantly improved both at 1 month (mean postoperative BAD score 24.9 ± 6.7 , $p < 0.01$) and at the last follow-up (mean last BAD score 28 ± 4.8 , $p < 0.01$; mean follow-up 40.6 ± 30 months) as compared to the total SD BAD scores (mean 31.3 ± 0.8 ; Table 3). The effect of surgery was not correlated with baseline dystonia duration ($r = 0.17$, $p > 0.05$) or time spent in SD before the final surgery ($r = 0.19$, $p > 0.05$). Overall clinical outcomes categorized according to the modified Ben-Haim scale at the 1-month follow-up and the subjective benefit reported by caregivers are shown in Fig. 1. No further SD recurrence was noted during follow-up. Mortality as a direct consequence of an SD episode was 7.1% (1/14), while 2 other patients (2/14 [14.3%]) died during follow-up due to complications indirectly related to the underlying dystonia. They both suffered from a severe form of pneumonia evolving into sepsis.

Deep Brain Stimulation

Bilateral GPi DBS was performed in 8 patients, ending

TABLE 2. Patient demographics, baseline dystonia characteristics, and initial drug treatment for SD

Case No.	Sex	Age at Diagnosis (yrs)	Dystonia Etiology	Dystonia Course	Baseline BAD Score	Age at SD Onset (yrs)	Trigger Factors	SD Phenomenology	Initial Pharmacological Treatment
1	F	2	PKAN classic	Progressive	28	10	ITB pump infection	Tonic	Midazolam, propofol, tetrabenazine, trihexyphenidyl
2	F	4	Post-infective	Static	24	7	Bacterial infection	Tonic	Midazolam, propofol, tetrabenazine, oral baclofen
3*	M	1	Unknown	Slow progressive	22	9	Pyrexia of unknown etiology	Phasic	Phenobarbital, oral baclofen, trihexyphenidyl, quetiapine, midazolam
4*	F	1	GNAO1	Progressive	19	6	Dental infection	Phasic	Midazolam, tetrabenazine, oral baclofen
5	M	2	PKAN atypical	Static	22	8	ITB pump malfunction	Tonic	Midazolam, propofol, tetrabenazine
6	F	3	CP	Static	20	10	Viral infection	Phasic	Midazolam, propofol, tetrabenazine, oral baclofen
7	M	6	CP	Static	22	14	None	Tonic	Midazolam, propofol, trihexyphenidyl
8	M	11	PKAN classic	Progressive	12	13	None	Tonic	Midazolam, propofol, trihexyphenidyl
9	M	4	PKAN classic	Progressive	22	9	None	Tonic	Midazolam, propofol, tetrabenazine, oral baclofen
10	F	2	PKAN classic	Progressive	21	10	None	Tonic	Midazolam, propofol, tetrabenazine
11	F	16	PKAN classic	Progressive	22	24	Bacterial	Tonic	Midazolam, propofol, tetrabenazine
12†	F	1	CP	Static	25	19	None	Phasic	Midazolam, propofol, tetrabenazine
13*	F	1	GNAO1	Progressive	24	10	None	Phasic	Midazolam, propofol, trihexyphenidyl
14†	M	2	CP	Static	22	16	None	Tonic	Midazolam, propofol, thiopentone, tetrabenazine, trihexyphenidyl

CP = cerebral palsy; GNAO1 = guanine nucleotide-binding protein, alpha-activating activity polypeptide O; PKAN = pantothenate kinase-associated neurodegeneration.

* These 3 patients had a previous SD, managed with antidystonic drugs and sedation.

† These 2 patients died during the follow-up due to complications unrelated to their baseline dystonia.

TABLE 3. Surgery for SD and outcomes

Case No.	Type of Surgery	SD BAD Score	Postop BAD Score	Last BAD Score	Time From SD Onset to Surgery (days)	SD Resolution After Surgery (days)	Modified Ben-Haim Scale	Caregiver Benefit Assessment Scale	Complications	FU (mos)
1	Pallidotomy	32	32	NA	60	Death after 35 days	1	-1	NA	NA
2	Pallidotomy	32	29	31	43	1	2	2	None	12
3	Staged pallidotomy	30	14	15	36	35	4	3	None	12
4	DBS	32	21	21	15	24	3	2	None	12
5	Pallidotomy	31	30	30	3	15	2	0	None	12
6	DBS	32	22	22	15	33	3	2	Lead fracture	63
7	DBS	31	25	25	40	30	3	3	Lead fracture	19
8	DBS	32	9	24	15	2	4	3	None	84
9	DBS	31	28	28	15	15	2	2	None	36
10	DBS	30	28	28	9	40	2	2	Lead fracture	42
11	DBS	32	30	25	63	60	2	2	None	28
12*	Pallidotomy	31	24	28	60	50	3	0	None	38
13	DBS, pallidotomy	32	28	28	30	60	3	3	None	180
14*	Pallidotomy	30	25	28	21	8	3	0	None	30

NA = not applicable.

* Two patients died during the follow-up due to complications unrelated to their baseline dystonia.

FIG. 1. A: Overall motor outcomes at the 1-month follow-up after surgery, categorized according to the modified Ben-Haim scale. **B:** A subjective assessment of the surgical procedures was administered to all caregivers during a telephone interview in June 2018 to capture potential easing of caregiving and increased patient comfort levels after surgery in the long term. Among the patients experiencing a good or excellent benefit (red and yellow), 70% underwent DBS surgery. Figure is available in color online only.

the storm in 87.5% (7/8) of cases (Table 3). The mean SD resolution time among these patients was 34.8 ± 19 days. Stimulation was usually started 2 days after surgery, set at the following parameters: double monopolar symmetric stimulation (case+, 1–, 2–), 2.5–4 V, 60–90 μ sec, and 130–185 Hz.

After 6 months, 1 patient showed a progressive slight dystonia worsening. After a readjustment of stimulation parameters, the patient's condition immediately improved, and dystonia returned to its baseline characteristics in a few days. In another patient, GPi DBS provided no benefit at all. She then underwent rescue conventional pallidotomy with SD regression.

No immediate postoperative adverse events were observed following DBS surgery, but there were a few hardware-related complications during the long-term follow-up. Three patients (3/8 [37.5%]) had fatigue fracture of the right extracranial lead. They showed acute worsening of

the baseline dystonia and consequently underwent urgent lead replacement.

Pallidotomy

Pallidotomy was the first surgical option in 6 patients (Table 3). Of these, 5 underwent conventional bilateral pallidotomy and 1 had bilateral SP. Pallidotomy interrupted SD in 5 patients (5/6 [83.3%]) and was ineffective in 1 patient who eventually died after 1 month. Resolution of the storm among these patients took a mean 21.8 ± 20.2 days. No further neurological deficits or complications were observed after the surgeries. In addition, 1 patient successfully underwent pallidotomy as a last-resort treatment after GPi DBS failure.

DBS Versus Pallidotomy

Repeated measures ANOVA showed no significant dif-

FIG. 2. Repeated measures ANOVA of BAD scores (y-axis) showing no significant differences between the surgical procedures ($p > 0.05$). fu = follow-up; pre = preoperatively; post = postoperatively. Figure is available in color online only.

ference in BAD scores between the DBS and pallidotomy groups (p for interaction term > 0.05 ; Fig. 2). Similarly, no significant differences were observed between the two techniques in terms of failure rates (risk difference DBS vs pallidotomy -0.03 , 95% CI -0.36 to 0.30) or in terms of SD resolution time after surgery (DBS 34.8 ± 19 days, pallidotomy 21.8 ± 20.2 days, $p > 0.05$)

Postoperative Lead and Lesion Localization

The mean stereotactic atlas coordinates in relation to

the midcommissural point confirmed that lesions were usually located slightly anteromedially as compared to the lead location (Fig. 3). All 16 DBS leads were successfully localized in the MNI space, and all cases had at least 1 contact within the border of the posteroventral GPi.

Discussion

Review of the Literature

As far as we know, this is the first single-center evaluation to report both GPi DBS and pallidotomy outcomes for the treatment of drug-resistant SD. To date, 30 GPi DBS and 8 ablative pallidotomy procedures have been separately described as isolated case reports, with varying success rates (Table 4).^{2–4,6,7,11,14,19,21–23,28,30,34,40,41,44,45}

Ablative procedures, such as thalamotomy and pallidotomy, were the first surgical treatments used in SD patients.³⁷ In 1998, Manji et al. performed for the first time 2-stage ventrolateral thalamic nuclei lesioning in a 9-year-old boy with severe SD and a unilateral left thalamotomy in a 38-year-old woman affected by a prevalent right-sided severe postencephalitic hemidystonia.²⁶ In subsequent years, pallidotomy was found to be effective in the treatment of L-dopa–induced dyskinesia in patients with advanced Parkinson’s disease; thus, the main target of stereotactic ablative procedures shifted from the thalamus to the GPi in dystonic patients as well.⁹ Currently, a larger study on SD and pallidotomy has been reported by Marras et al., who described the indications, surgical strategy, and outcome of bilateral pallidotomy in 4 pediatric patients with secondary dystonia who developed sudden refrac-

	X	Y	Z
• Right DBS lead	20.19 ± 2.08	2.78 ± 0.78	- 5.39 ± 1.02
• Right Pallidotomy	16.52 ± 1.67	4.45 ± 1.72	- 3.81 ± 1.22
• Left DBS lead	18.69 ± 1.54	1.96 ± 0.76	- 5.34 ± 1.32
• Left Pallidotomy	16.63 ± 2.45	3.21 ± 1.90	- 3.86 ± 1.21

FIG. 3. **Upper:** Postoperative DBS lead locations in the MNI space. GPi, green; globus pallidus externus, blue; subthalamic nucleus, orange; red nucleus, red. **Lower:** DBS lead and pallidal lesion localizations in the AC-PC space. Figure is available in color online only.

TABLE 4. Literature review on DBS and pallidotomy for the treatment of SD

Authors & Year	Procedure	No. of Patients	Type of Dystonia	Age at Dystonia Onset	Trigger Factors	Age at SD	Time to Surgery	Outcome Reported	Complications From Surgery
Coubes et al., 1999	DBS	1	GD DYT1-	3 yrs	None	8 yrs	2 mos	SD resolution after 6 wks	None
Angelini et al., 2000	DBS	1	NS	5 mos	None	13 yrs	NR	Extubation w/in 1 wk, pharmacological therapy discontinued after 3 wks, walking independently after 7 mos	None
Teive et al., 2005	DBS	1	Primary craniocervical dystonia	NS	"Stress"	NR	NR	Improvement above baseline	Mild Lt hemiparesis
Zorzi et al., 2005	DBS	3	GD DYT1-	1.6 yrs	None	8.2 yrs	4 mos	Sedation discontinued at 3 mos, improved	IPG turned off inexplicably
			GD DYT1-	3 yrs	None	10.6 yrs	6 mos	SD resolution in 2 days, improvement	IPG turned off inexplicably
			Idiopathic encephalopathy	6 mos	Urinary infection	14.2 yrs	2 mos	SD resolution in 1 wk, no improvement	None
Borggraefe et al., 2008	DBS	1	DYT1+	7 yrs	None	14 mos	NS	Improvement above baseline after 4 mos	None
Elkay et al., 2009	DBS	1	Batten's disease	17 yrs	None	19 yrs	NR	Improvement after unsuccessful pallidotomy	None
Jech et al., 2009	DBS	1	GD DYT1-	8 yrs	None	11 yrs	2 wks	Extubated after 45 days, sedation for 70 days, marked improvement	None
Martinez-Torres et al., 2009	DBS	1	GD DYT3+	33 yrs	None reported	34 yrs	NR	"Immediate improvement after surgery"	None
Timmerman et al., 2010	DBS	2	PKAN	4 yrs	None reported	14 yrs	"Emergency DBS"	Death after 6 wks from surgery	Death
			PKAN	8 yrs	DBS surgery	17 yrs	1 day after DBS surgery	SD resolution after "several days of stimulation" w/ improvement above baseline	Open femur fracture from SD
Apetaurova et al., 2010	DBS	2	CP	"Early age"	Metoclopramide	NS	4 mos	Extubation w/in 1 day, unchanged from baseline	None
			CP	NS	Surgery (omentectomy)	NS	2 mos	Extubation w/in 2 days, unchanged from baseline	None
Grandas et al., 2011	DBS	1	PKAN	13 yrs	None reported	19 yrs	3 days	Improvement above baseline after a few days	None
Kovacs et al., 2011	DBS	1	Tardive dystonia	17 yrs	None reported	18 yrs	1 mo	Improvement above baseline after a few days of stimulation	None
Walcott et al., 2012	DBS	3	CP	NS	Surgical infection	14 yrs	1 mo	Extubation after a few days, improved at the 1-yr FU	Lt lower contacts not functioning properly
			GD	NS	None reported	9 yrs	4 mos	Discharge home 6 wks after surgery	IPG infection w/ system explantation on the rt
			CP	NS	Pulmonary illness	9 yrs	2 mos	Improvement at the 3-mo FU	None

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TABLE 4. Literature review on DBS and pallidotomy for the treatment of SD

Authors & Year	Procedure	No. of Patients	Age at Dystonia			Trigger Factors	Age at SD	Time to Surgery	Outcome Reported	Complications From Surgery
			Type of Dystonia	Onset						
Ben-Haim et al., 2016	DBS	5	GD DYT1+	6 yrs	Abdominal surgery	13 yrs	14 days	Complete recovery	None	
			GD DYT1+	8 yrs	DBS infection	11 yrs	2 days	Improved from baseline	Postop pneumonia	
			GD DYT1+	7 yrs	DBS surgery	8 yrs	5 days	Improved from baseline	None	
			GD DYT1+	7 yrs	DBS lead fracture	15 yrs	4 days	Return to baseline	None	
			GD DYT1+	8 yrs	Abdominal distress	11 yrs	131 days	Improved from baseline	None	
Oterdoom et al., 2018	DBS	1	GD DYT6+	3.5 yrs	Constipation	11 yrs (previous GPI DBS 15 mos before)	4 wks (lead reposition)	Improvement after 1 wk	None	
Lobato-Polo et al., 2018	DBS	5	Idiopathic	41 yrs	None	41 yrs	17 days	Improvement after 3 days	Delirium	
			CP	1 mo	Respiratory infection	8 yrs	8 days	Improvement after 21 days	None	
			Idiopathic	41 yrs	Medication tolerance	41 yrs	36 days	Improvement after 1 day	Behavioral changes	
			CP	1 yr	Displacement of DBS lead	10 yrs	3 days	Improvement after 7 days	Infection (no hardware removal)	
			GCH1 mutation	7 yrs	Medication change	32 ys	6 days (STN DBS)	Improvement after 1 day	None	
Teive et al., 2005	Pallidotomy	1	CP	NR	None	8 yrs	NR	Excellent	None	
Balas et al., 2006	Pallidotomy	1	HSD	5 yrs	None	10 yrs	NR	"Immediate postoperative improvement" after bilateral pallido-thalamotomy	None	
Elkay et al., 2009	Pallidotomy	2	Batten's disease	9 yrs	None	21 yrs	NR	Marked improvement after 10 days	None	
			Batten's disease	17 yrs	None	19 yrs	NR	Improvement for only 3 wks, requiring subsequent GPI DBS	None	
Marras et al., 2014	Pallidotomy	4	Chromosomopathy	3 yrs	Mononucleosis	13 yrs	2 mos	SD resolution after 40 days	None	
			Encephalopathy	1 mo	Fever	17 yrs	14 days	SD resolution w/in 1 mo	None	
			Idiopathic bilateral striatal necrosis	4 mos	Enteritis	5 yrs	50 days	SD resolution after 3 wks	None	
			CP	8 mos	None	10 yrs	60 days	SD resolution after 2 mos	None	

GD = generalized dystonia; HSD = Hallervorden-Spatz disease; IPG = internal pulse generator; NR = not reported; NS = not specified; STN = subthalamic nucleus.

tory SD.²⁸ In their series, pallidotomy was performed in the midportion of the GPi (X: 14–18, Y: 3–5, Z: –2) with progressive improvement of dystonia in all patients without any observed recurrence at a mean follow-up of 18.2 months. No postoperative complications were noted.

As with ablative surgical methods, the number of SD patients treated with GPi DBS is still limited. The first instance of bilateral GPi stimulation for SD was reported in 1996 by Philippe Coubes, who knew of the great efficacy of Laitinen's posteroventral pallidotomy for parkinsonian dyskinesias and thus proposed GPi stimulation as a compassionate intervention in an 8-year-old girl who had been in a complete refractory dystonic storm for several weeks.¹¹ The striking result obtained by Coubes caused him to apply GPi DBS in 7 patients with *DYT1* generalized dystonia, opening the way for the surgical treatment of many other types of dystonia.¹² In 2016, a review by Ben-Haim et al. found that of the 28 SD patients described in the literature who had been treated with DBS or ablative surgery, 26 had cessation of their dystonic crisis with a return to baseline function and, in most cases, clinical improvement.⁶ Since then, a growing number of reports describing the effectiveness of DBS in cases of SD have been published because of the increased availability of the technique worldwide along with its great popularity for the treatment of other movement disorders, such as Parkinson disease and tremor (Table 4). Recently, Nerrant and colleagues retrospectively analyzed a cohort of 328 dystonia patients who had been seen over a period of 20 years.³² Twenty-five of these patients underwent de novo DBS to control an ongoing SD episode, with resolution in 92% of them, whereas 9 patients underwent subsequent lead implantation as rescue therapy while already benefiting from DBS, with a success rate of 91.3%. Mortality as a direct consequence of an SD episode that was refractory to medical treatment and DBS was 10%.

Overall Efficacy of Surgery for the Treatment of Drug-Resistant SD

In our series, the per-procedure success rate of surgery (86.7% [13/15] success rate; 1 patient required salvage pallidotomy after DBS failure) was in line with rates previously reported in the literature on the subject.^{6,15} In addition, the positive effect of surgery was independent of the baseline dystonia duration and the time spent in SD before surgical intervention. In contrast with previously published experiences, only 2 patients in our study showed mild improvement in their baseline dystonic conditions, with dystonic conditions remaining unchanged or even worsening in the other patients (Fig. 1).^{6,23} This difference in results may be due, in part, to the great heterogeneity of baseline dystonia traits or SD characteristics among studies. Follow-ups are also highly variable among studies, and only a few papers have reported long-term motor outcomes. Recently, Elkaim et al. showed that the grade of motor improvement is not very predictable after surgery for SD.¹³ Patients who had undergone surgical intervention, in fact, showed improvement compared to pre-SD baseline in 65.5% of cases, with the other cases (34.5%) remaining unchanged or even worsening. These data are not negligible, especially if they are compared to the out-

standing long-term surgical motor outcomes reported for the general dystonic population.³¹

In our opinion, SD should be considered more than a transient event overlapping the baseline dystonia. It may be indicative of an evolution of the disease causing high instability of the basal ganglia–cortical network, which is hard to revert.

Given our data, DBS or pallidotomy seems to be effective in down-regulating this instability in the acute phase of SD but with poor results in the long term. Why this happens is difficult to explain. In our opinion, this question may find an exhaustive answer only after collecting a large amount of electrophysiological data on SD, allowing those in the field to better understand the complex and still unknown pathophysiology of the disease. In order to do this, however, considering the rarity of the disease, international cooperation among multiple centers is of paramount importance.

DBS Versus Pallidotomy

Bilateral GPi DBS and pallidotomy were successful in 87.5% and 83.3% of SD cases, respectively. In terms of postoperative BAD values, no significant differences were found between the two techniques. Pallidotomy resulted in a shorter time to SD resolution than that following DBS (21.8 ± 20.2 and 34.8 ± 19 days, respectively); however, the difference between the two techniques in this regard was not significant, although it nevertheless seems reasonable. DBS is, in fact, a pure neuromodulation technique that reestablishes neuronal networks' electrical stability over time. It is well known, for instance, that the effect of DBS in uncomplicated dystonia usually takes weeks to months to appear. Conversely, pallidotomy may work by anatomically interrupting an unregulated and disruptive circuit, allowing the remaining structures and circuits to function more properly in a shorter time.^{38,43}

Although both procedures were extremely safe in terms of intraoperative complications and postoperative neurological deficits, DBS was associated with an increased number of long-term hardware failures (37.5%). This finding is not surprising given that pallidotomy does not require implantation of permanent devices.

With regard to the postoperative location of pallidal lesions, our data suggest that lesioning a slightly more anteromedial portion of the GPi is equally safe, feasible, and effective as the ablation of the classic posteroventral DBS target. In our opinion, these data may be of some utility in the future considering that new, minimally invasive lesioning techniques, such as focused ultrasound, could soon be applied to dystonia and SD as well.

DBS showed greater subjective benefit among caregivers than pallidotomy (good and excellent benefit with DBS 70%, vs 30% with pallidotomy). However, these data should be considered with caution given that 3 deaths occurred in the pallidotomy group (1 directly related to SD and the other 2 from a severe form of pneumonia evolving into sepsis). In particular, the 2 deaths occurring during the follow-up period may have introduced an important bias influencing the final caregivers' evaluations. In addition, pallidotomy, as a permanent lesional procedure, may have raised unrealistic caregiver expectations. Finally, it is

not possible to exclude the fact that the anteromedial location of the lesions generated adverse events that the motor scale score and clinical evaluations were unable to detect. All of these points are purely speculative, however, and the low numbers of our sample do not allow for any definitive conclusions in this respect.

Study Limitations

This study has several limitations because of the unusual features of the pathological condition considered. First, the retrospective and nonrandomized design of the study may have introduced several forms of bias. More severe forms of SD may have been treated only with pallidotomy rather than DBS, thus hampering pallidotomy outcomes. In addition, the two populations are not strictly comparable because the target chosen for DBS is different from the one used for pallidotomy. Pharmacological therapies attempted before surgery were quite heterogeneous, and this could have strongly influenced the outcome after DBS and pallidotomy. Another important limitation of the study is the small sample size, which did not allow us to reach adequate statistical power. This could have definitely biased our statistical analysis.

Conclusions

SD is a rare, life-threatening emergency that can complicate a wide range of pediatric and adult dystonias. In this context, both GPi DBS and pallidotomy are effective, safe, and life-saving therapies and should be proposed early in the treatment of SD. The choice between the two procedures, in our opinion, should be tailored on a case-by-case basis, depending on factors such as etiology and evolution pattern of the underlying dystonia and clinical conditions at the moment of SD onset.

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Disclosures

Dr. Levi is a medical advisor at Newronika S.R.L. (neurostimulator manufacturer), but this activity is not relevant to the paper.

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Conception and design: Levi. Acquisition of data: Levi, Zorzi. Analysis and interpretation of data: Levi, Zorzi. Drafting the article: Levi. Critically revising the article: Zorzi, Messina, Romito, Tramacere, Dones, Nardocci, Franzini. Approved the final version of the manuscript on behalf of all authors: Levi. Statistical analysis: Tramacere.

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