

# Pallidal stimulation for acquired dystonia due to cerebral palsy: beyond 5 years

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**Background and purpose:** There is increasing evidence that deep brain stimulation (DBS) of the globus pallidus internus (GPi) is effective in patients with idiopathic or inherited generalized dystonia. There is comparatively less experience about the effects of GPi DBS on acquired dystonia, particularly dystonia due to cerebral palsy (DCP). Clinical and demographic outcome predictors for DBS in dystonia syndromes are also poorly defined. Our aim was to examine the efficacy and safety of GPi DBS for the treatment of generalized DCP.

**Methods:** Fifteen patients with DCP up to 6.2 years after DBS surgery were studied. Only mild limb spasticity or mild static brain magnetic resonance imaging abnormalities were acceptable for inclusion. Dystonia severity and disability were assessed by the Burke–Fahn–Marsden dystonia rating scale (BFMDRS), and health-related quality of life was assessed by the Short Form General Health Survey (SF-36) scale. The amount of energy delivered was calculated, and adverse events and side effects were collected.

**Results:** At last follow-up, BFMDRS motor score improved on average by 49.5%, and the disability score improved by 30%. Health-related quality of life improved in most patients. Age at implant, age at onset and disease duration did not correlate to outcome, whilst higher pre-operative dystonia severity and occurrence of spasticity were associated with poorer outcome. The patients received a stable amount of energy after the first 2 years post-implant and throughout all the observation period. There were few serious adverse events or side effects.

**Conclusions:** The outcome was encouraging in the majority of DCP patients, with a stable outlook and a good safety profile.

## Introduction

There is increasing evidence that deep brain stimulation (DBS) of the globus pallidus internus (GPi) is effective in patients with segmental or generalized dystonia [1]. Patients with idiopathic or inherited generalized dystonia have sustained motor response to GPi

DBS [2], but there is comparatively less experience on the efficacy and safety of GPi DBS on acquired dystonias. It has been reported that patients with tardive dystonia have sustained motor benefit by GPi DBS [3], whereas heterogeneous results have been reported in patients with acquired dystonia due to cerebral palsy (DCP) [4]. The studied patients presented variable combinations of dystonia and spasticity and received GPi implants at different ages spanning from late childhood to adulthood [5–8]. Predictors of outcome are needed for DCP: severity of dystonia and spasticity influence post-surgery outcome [4], but the role of other variables such as age at onset, duration of symptoms or age at time of surgery needs to be elucidated.

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A homogeneous group of patients with DCP who received a bilateral GPi implant were selected. The efficacy and safety of the procedure are reported and compared with earlier short-term data on similar patients.

## Methods

### Study design

All patients with DCP secondary to neonatal hypoxic or ischaemic encephalopathy were selected for GPi implant at the Carlo Besta Neurological Institute if they had persistent dystonia, isolated or combined only with mild spasticity, onset in infancy, generalized distribution and a static course [9]. On Axis II there were only mild static lesions or no degeneration or structural lesions [9]; dystonia was acquired, symptomatic to cerebral palsy [10]. A brain lesion was considered static only if no change was evident in repeated brain magnetic resonance imaging (MRI) performed before the implant. Static lesions were rated as mild when brain T1-weighted MRI abnormalities showed no more than decreased grey–white matter contrast with partial disappearance of the basal ganglia or minimum atrophy of the globus pallidus or putamen or when brain T2-weighted MRI abnormalities showed slight basal ganglia abnormalities without cortical involvement. As an additional inclusion criterion there were no cognitive (Mini-Mental State Examination score >24) or psychiatric abnormalities. Spasticity was rated as mild when the modified Ashworth score [11] was <2 in any segment.

The study was approved by the internal review board of the Carlo Besta Neurological Institute (registered at the Office for Human Research Protections as IORG0006168) and was carried out according to the Declaration of Helsinki. Informed written consent was obtained either from the patients or from their legal representative.

### Data collection

Dystonia severity was assessed at 1–3 months after implant and then at yearly intervals using the motor section of the Burke–Fahn–Marsden dystonia rating scale (BFMDRS) [12]. The time required to reach the maximal motor benefit after implant was recorded. Disability was assessed using the disability section of the BFMDRS [12], whilst health-related quality of life was assessed with a validated Italian version of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36) questionnaire [13].

Cognitive evaluation was performed at baseline and post-operatively at yearly intervals by assessing the following domains: global cognition, memory, executive functions, verbal fluency and attention. The occurrence of psychiatric disorders was assessed at baseline by administering the Brief Psychiatric Rating Scale [14]. Concomitant medication was reduced whenever possible after implant. Baclofen (administered intrathecally in two patients) was briefly reduced before implant without appreciable changes in dystonia severity and then left unchanged in order not to influence post-implant outcome.

Bilateral stereotactic implantation of DBS electrodes was performed in the ventroposterolateral portion of the GPi, according to a previously described procedure [15]. A quadripolar DBS electrode (DBS-3389; Medtronic Inc., Minneapolis, MN, USA) was used. Intra-operative test stimulation was performed in bipolar mode using contacts 0–3+ with a frequency of 130 Hz and a pulse width of 90  $\mu$ s. During the same surgical session the electrodes were connected to internal pulse generators (two Medtronic Soletra or two Medtronic active SC for each patient).

The location of the therapeutic contacts and the volume of tissue activated by the electrical field around them was ascertained by combining the findings of the Medtronic StealthStation TREON plus Navigation System with the findings of Medtronic Optivise™ software. Three-dimensional anatomy of basal ganglia was adapted to the brain geometry of each patient by overlaying the pre-operative and post-operative MRI or computed tomography scan onto the software atlas. This procedure was done by a neurosurgeon blinded to the results of neurostimulation in each patient. The volume of activated tissue was estimated by using the contact(s) and the electrical parameters set when the patient had reached a stable clinical condition. Electrodes were considered as correctly positioned only if the electrode contacts, the electric field volumes around the stimulated contacts, or both, included the GPi.

Stimulation started shortly after surgery. Stimulation settings were recorded 1–3 months after implant and then at yearly intervals with stimulation turned on. The total electrical energy delivered (TEED) through the electrodes (measured in  $\mu$ J) was computed using the formula  $TEED = (\text{amplitude}^2 \times \text{pulse width} \times \text{frequency rate}) / \text{impedance}$  [16]. Adverse events and side effects were collected and classified, according to a previous report [17], as transient, persistent, stimulation-induced, device-related, or unrelated to the procedure or stimulation. A structured questionnaire was used in order to avoid reporting

bias, as already noted for DBS in Parkinson disease [18].

### Statistical analysis

Normality of data distribution was tested using a Kolmogorov–Smirnov test. Analysis of variance for repeated measures was used to compare motor scores between baseline and the different follow-ups in the patient series, in order to evaluate the motor efficacy of DBS and the variation of stimulation settings; Bonferroni's correction was applied. Since not all patients reached the same time point, data comparing baseline and post-operative motor scores were analyzed by means of the Wilcoxon signed-rank test for matched pairs. A pair represented data obtained in a single individual at yearly intervals compared with baseline.

Given the explorative nature of this study, the standard non-corrected significance  $\alpha$  level of  $P < 0.05$  was used to reduce the risk of a type II error. All values were expressed as mean  $\pm$  SD. The Mann–Whitney  $U$  test for unmatched samples was used to compare the motor score and the percentage of improvement between the patients with abnormal or normal brain MRI and between the patients with occurrence of spasticity or not.

Pearson's correlation test was used to test for prognostic demographic and pre-operative factors for treatment outcome. A statistical threshold of  $P < 0.05$  (two-tailed) was considered to be significant.

All data were then entered into a database in an anonymous format according to the Italian data protection law. Statistical analysis was performed using Stata-Soft STATISTICA software (<http://www.statsoft.com>, release 7.0).

## Results

Fifteen patients (seven males and eight females) were included in the study. Their demographic and baseline features are listed in Tables 1 and S1. Thirteen patients had a history of perinatal hypoxic encephalopathy, whilst patients 2 and 7 had a history of kernicterus; there was otherwise no evidence for other causes of acquired dystonia. Concomitant pre-operative and post-operative medications are reported in Table S1; this concomitant treatment was reduced (particularly anticholinergics and levodopa) or remained unchanged in most patients.

The implant was performed in adult age (on average at 29.8 years) and dystonia was generalized in all cases. Nine patients had also mild limb spasticity: in five of them spasticity was generalized, in three patients it was unilateral and in one it involved a sin-

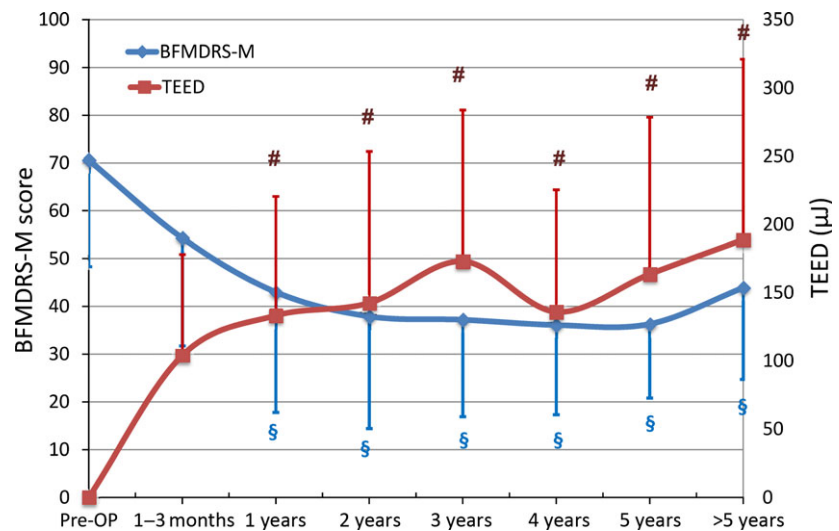
gle lower limb. In seven patients there was no evidence of degeneration or structural lesion, whereas eight had MRI evidence of a static lesion: putaminal atrophy in three, thalamic abnormalities in three, signal abnormalities in the basal ganglia in two (Table S1, Fig. S1). The patients were followed up for at least 2 years after DBS (on average, for 4.4 years).

There was no difference in age at onset, age at implant and baseline motor severity between patients with or without MRI abnormalities or between patients with or without limb spasticity. BFMDRS motor score improved by an average of 41% at 1 year, by 48% 2 years after implant, and by 49.5% at the last visit (Fig. 1, Table 2). The time of maximal motor improvement was  $1.7 \pm 0.9$  years after implant. Outcome was not uniform amongst patients. Patients 13 and 14 had a remarkable motor improvement (approximately 80% on the BFMDRS) at 2 years that partially relapsed to stabilize around 42% at the last follow-up visit. One further patient had less than 30% improvement and one only 17%. Nine patients improved remarkably after surgery and retained such improvement throughout the follow-up. All body segments were improved although unevenly 2 years after implant and remained improved until the last visit (Table 2). Motor outcome and TEED also stabilized from the second year post-implant until the last visit (Fig. 1). There were no differences in motor outcomes or TEED between patients with or without brain MRI abnormalities and between patients with or without spasticity.

The severity of dystonia at baseline was inversely correlated to outcome measured 3 years after implant ( $P = 0.027$ ) and at the last visit ( $P = 0.003$ ), whereas demographic variables, such as age at implant, age at onset and disease duration, and occurrence of MRI abnormalities had no influence. Occurrence of spasticity was also a negative predictor of outcome measured 2 years after implant ( $P = 0.037$ ), 3 years after implant ( $P = 0.018$ ) and at the last visit ( $P = 0.004$ ).

The TEED was progressively increased, starting 3 months after surgery, mainly due to increase in amplitude (Fig. 1). Average parameters at 2 years were voltage  $3.0 \pm 0.5$  V, pulse width  $111.2 \pm 42.2$   $\mu$ s, frequency  $132.5 \pm 17.4$  Hz, impedance  $931 \pm 423.4$   $\Omega$  and TEED  $142.5 \pm 111.0$   $\mu$ J. The parameters at the last follow-up visit were voltage  $3.1 \pm 0.7$  V, pulse width  $111.4 \pm 38.1$   $\mu$ s, frequency  $132.6 \pm 19.5$  Hz, impedance  $968.4 \pm 440.3$   $\Omega$  and TEED  $138.8 \pm 122.2$   $\mu$ J. TEED values stabilized 2 years after implant, with some degree of fluctuation afterwards (Fig. 1). No correlation was found between motor improvement and TEED. Twelve patients received at least one implantable pulse generator

**Figure 1** Time-course of motor outcome measured by the Burke–Fahn–Marsden dystonia rating scale (mean score  $\pm$  SD) and of total electrical energy delivered (mean TEED  $\pm$  SD). Significance levels are as follows: §,  $P < 0.05$  compared to pre-operative score; #,  $P < 0.05$  compared to values measured 1–3 months post implant.



change, due to exhausted batteries; the average duration of the implantable pulse generator battery was  $55.9 \pm 17.9$  months.

The BFMDRS disability score improved by an average of 22% 1 year and 25% 2 years after implant, and 30% at the last visit (Table 2). There was no correlation between pre-operative and post-operative BFMDRS disability scores. Health-related quality of life, as assessed by the SF-36 scale, improved in most patients (Table 1), particularly concerning physical functioning, physical and emotional roles, social functioning, body pain and the vitality subscores of the SF-36 scale (Table S2). There were no neuropsychological deficits or psychiatric disorders before GPi implant. In the post-operative follow-up, no patient developed cognitive impairment or psychiatric disorders.

The location of the stimulating contact and the volume of activated area are reported for all patients in Fig. S2. Fourteen patients were deemed to be optimally targeted (i.e. the leads were implanted bilaterally in the posteroventrolateral region of the GPi); in patient 5 the therapeutic contacts of the left lead laid outside the boundaries of the GPi, and indeed no beneficial effect was obtained (relative variation 17%). Patients 2 and 7 had DCP secondary to kernicterus and improved significantly on both motor and functional subscores.

The safety profile of the procedure is reported in Table 3. One patient suffered extracranial lead damage following head trauma, one had an unexplained lead migration and one had hardware infections. In all of them lead/hardware re-implant or appropriate medical therapy resolved the problem. Hardware-related complications included unexplained switching-off of one pulse generator, leading to significant acute

motor worsening in one patient. Patient 10 died 2.4 years after implant due to acute cardiac failure unrelated to neurological or post-operative issues.

## Discussion

A naturalistic series of adult patients with acquired generalized DCP implanted and followed in a single center according to a consistent set of criteria are reported. In this series, GPi DBS provided a sustained improvement of motor symptoms starting from 2 years after implant. All the patients had severe dystonia without cognitive impairment and some had mild static brain MRI abnormalities. Surgery was performed in adult age, on average around 30 years, with the youngest patient implanted at 15 years and the oldest at 47 years. The magnitude of improvement was unevenly distributed amongst patients: nine had a remarkable improvement lasting throughout follow-up for more than 4.6 years with seven of them reaching a 50% BFMDRS motor decrease, similarly to what has been reported for patients with idiopathic or inherited generalized dystonia in controlled studies [2, 19]. The observation that a minority of patients with DCP have insufficient improvement or relapse of dystonia has been previously mentioned in a shorter-term observation [8]. These earlier data are confirmed and expanded by evaluating a homogeneous single-center series for over 2 years after implant. Compared with a pioneering multicenter 1-year observation of DCP patients [8], better outcome and further improvement beyond 1 year are reported here. This probably depends on the homogeneity of patients and procedures in the present series. Our results are in keeping with a subset of six patients for whom there is no mention of misplacement or diffusion to the globus

**Table 1** Demographic and clinical features of individual patients in this series

| Patient    | Demographic data |                                    |                        |                                     | Phenomenology     | BFMDRS motor score |             | BFMDRS disability score |            | SF-36 score   |              |
|------------|------------------|------------------------------------|------------------------|-------------------------------------|-------------------|--------------------|-------------|-------------------------|------------|---------------|--------------|
|            | Gender           | Age of dystonia appearance (years) | Age at implant (years) | Disease duration at implant (years) | Follow-up (years) | Pre-operative      | Last visit  | Pre-operative           | Last visit | Pre-operative | Last visit   |
| 1          | F                | 2                                  | 31                     | 29                                  | 5                 | 45                 | 20          | 14                      | 8          | 351           | 633          |
| 2          | M                | 0                                  | 17                     | 17                                  | 3                 | 81                 | 59.5        | 20                      | 16         | 254           | 472          |
| 3          | F                | 0                                  | 15                     | 15                                  | 5                 | 80                 | 30          | 22                      | 17         | 254           | 555          |
| 4          | F                | 7                                  | 37                     | 30                                  | 3                 | 81                 | 23.5        | 24                      | 9          | 323           | 657          |
| 5          | M                | 1.5                                | 18                     | 16.5                                | 3                 | 67.5               | 56          | 27                      | 25         | 256           | 339          |
| 6          | M                | 0                                  | 34                     | 34                                  | 3                 | 77                 | 60          | 27                      | 21         | 293           | 490          |
| 7          | M                | 0                                  | 18                     | 18                                  | 6.2               | 104                | 59          | 28                      | 22         | 237           | 393          |
| 8          | F                | 0                                  | 31                     | 31                                  | 4.1               | 58                 | 20.5        | 21                      | 9          | 259           | 534          |
| 9          | M                | 8                                  | 27                     | 19                                  | 7                 | 39                 | 15          | 13                      | 8          | 318           | 546          |
| 10         | M                | 0                                  | 42                     | 42                                  | 2.2               | 109                | 45          | 29                      | 26         | 332           | 430          |
| 11         | F                | 10                                 | 36                     | 26                                  | 3                 | 37                 | 22.5        | 18                      | 10         | 250           | 554          |
| 12         | F                | 0                                  | 34                     | 34                                  | 7                 | 94.5               | 51.5        | 26                      | 22         | 229           | 464          |
| 13         | F                | 14                                 | 34                     | 20                                  | 6.4               | 59                 | 34          | 14                      | 10         | 277           | 445          |
| 14         | F                | 13                                 | 47                     | 34                                  | 6                 | 74.5               | 43          | 26                      | 18         | 306           | 477          |
| 15         | M                | 13                                 | 26                     | 16                                  | 2                 | 57.7               | 8           | 17                      | 6          | 283           | 657          |
| All series | 15 (7M/8F)       | 4.6 ± 5.6                          | 29.8 ± 9.5             | 25.4 ± 8.6                          | 4.4 ± 1.8         | 72.0 ± 22.7        | 36.6 ± 18.0 | 21.7 ± 5.5              | 15.1 ± 6.9 | 281.5 ± 37.4  | 509.7 ± 93.6 |

BFMDRS, Burke–Fahn–Marsden dystonia rating scale; P, phasic; T, tonic; P-T, phasic and tonic. Mean values ± SD are reported in the bottom row.

**Table 2** Burke–Fahn–Marsden dystonia rating scale scores and subscores before and after deep brain stimulation

|                              | Pre-operative | 3 months (n = 15)     | 1 year (n = 15)       | 2 years (n = 15)     | Last visit (n = 15)   |
|------------------------------|---------------|-----------------------|-----------------------|----------------------|-----------------------|
| Motor score                  | 72.0 ± 22.7   | 53.5 ± 25.2 (–25.7%)* | 42.3 ± 19.3 (–41.3%)* | 37.6 ± 22.9 (–47.8)* | 36.6 ± 18.0 (–49.1%)* |
| Eyes and mouth (0–16)        | 4.9 ± 3.2     | 3.2 ± 2.7 (–35.8%)*   | 3.5 ± 1.6 (–29.3%)*   | 1.9 ± 1.4 (–61.5%)*  | 2.3 ± 2.1 (–54.1%)*   |
| Speech and swallowing (0–16) | 9.1 ± 5.0     | 7.5 ± 5.2 (–17.5%)*   | 7.1 ± 3.2 (–21.6%)*   | 6.5 ± 3.6 (–28.5%)*  | 5.2 ± 3.8 (–43.1%)*   |
| Neck and trunk (0–24)        | 17.3 ± 5.6    | 12.0 ± 5.6 (–31.0%)*  | 9.7 ± 5.6 (–44.1%)*   | 9.4 ± 5.8 (–45.8%)*  | 7.8 ± 5.3 (–55%)*     |
| Upper limbs (0–32)           | 22.7 ± 7.8    | 17.5 ± 8.7 (–23.2%)*  | 12.6 ± 9.6 (–44.5%)*  | 11.7 ± 9.9 (–48.7%)* | 12.5 ± 10.1 (–45.2%)* |
| Lower limbs (0–32)           | 18.9 ± 9.7    | 13.4 ± 10.1 (–29.2%)* | 9.4 ± 6.7 (–50.3%)*   | 8.0 ± 7.8 (–57.7%)*  | 8.3 ± 6.7 (–56%)*     |
| Disability score             | 21.7 ± 5.5    | 19.2 ± 6.6 (–11.5%)*  | 17.0 ± 6.8 (–21.8%)*  | 16.2 ± 6.9 (–25.5%)* | 15.1 ± 6.9 (–30.4%)*  |
| Speech (0–4)                 | 3.1 ± 0.9     | 2.7 ± 1.1 (–12.9%)*   | 2.5 ± 1.3 (–17.4%)*   | 2.4 ± 1.2 (–21.7%)*  | 2.4 ± 1.3 (–21.7%)*   |
| Writing (0–4)                | 3.2 ± 0.9     | 2.8 ± 0.8 (–12.5%)*   | 2.5 ± 0.9 (–22.6%)*   | 2.3 ± 0.9 (–29.2%)*  | 2.3 ± 0.9 (–29.2%)*   |
| Feeding (0–4)                | 2.8 ± 0.9     | 2.5 ± 1.0 (–10.7%)*   | 2.1 ± 1.0 (–23.8%)*   | 2.0 ± 0.9 (–28.6%)*  | 1.9 ± 0.9 (–33.3%)*   |
| Eating and swallowing (0–4)  | 1.7 ± 0.7     | 1.5 ± 0.9 (–11.6%)*   | 0.7 ± 0.9 (–57.7%)*   | 0.8 ± 0.8 (–53.8%)*  | 0.5 ± 0.8 (–69.2%)*   |
| Hygiene (0–4)                | 3.3 ± 1.0     | 3.0 ± 1.0 (–9.0%)*    | 2.9 ± 1.2 (–12.0%)*   | 2.7 ± 1.3 (–18.0%)*  | 2.5 ± 1.3 (–26.0%)*   |
| Dressing (0–4)               | 3.2 ± 0.9     | 2.9 ± 1.1 (–9.3%)*    | 2.6 ± 1.1 (–18.8%)*   | 2.5 ± 1.1 (–22.6%)*  | 2.3 ± 1.1 (–29.2%)*   |
| Walking (0–6)                | 4.4 ± 1.4     | 3.8 ± 1.7 (–13.6%)*   | 3.6 ± 1.6 (–18.2%)*   | 3.5 ± 1.7 (–21.2%)*  | 3.3 ± 1.6 (–24.2%)*   |

\*Statistically significant from baseline ( $P < 0.05$ ); \*\*statistically significant from baseline ( $P < 0.01$ ).

pallidus externus, who had a 45.8% improvement in the multicenter study [8]. Our results are also in keeping with a recent report by Kim *et al.* [5], who found a 1-year motor improvement of 50.4% and a 2-year improvement of 40% after GPI implant in seven adult patients with DCP. The magnitude of improvement observed in the present series of acquired dystonia cases approaches the reported improvement for isolated generalized dystonia cases (idiopathic or inherited) [2].

Our results on patients 2 and 7 with DCP secondary to kernicterus who presented a significant motor improvement are encouraging, particularly considering the paucity of data on outcome for this acquired dystonia subtype. Two case reports [6, 20] are in keeping with our finding, as they mention a motor improvement of 32.9% in an adult 24 months after GPI implant and of 47.2% in a child 4.5 years after GPI implant. In our series, patient 2 had a normal brain MRI, whereas patient 7 presented evidence of slight chronic basal ganglia (mainly pallidal) MRI changes. Taking together this and a similar earlier observation showing comparable MRI changes [20], it can be considered that slight MRI abnormalities do not represent a contraindication for GPI implant. Further studies are warranted on this type of patient.

The identification of demographic or clinical predictors of outcome for patients with DCP who undergo GPI DBS is an important clinical need, particularly considering that acquired dystonia has a higher degree of variability compared with inherited or idiopathic forms. It is reported that pre-operative dystonia severity and occurrence of spasticity are two negative predictors of outcome for GPI surgery, in keeping with a recent meta-analysis [4]. The long-term follow-up allowed us to observe here that improvement stabilizes around 2 years after implant, suggesting that previous reports with 1 year or less of post-implant follow-up may not have captured the complete treatment effects [7, 8]. It has been previously suggested that patients with ‘phasic’ dystonic movements had better outcomes than patients with prevalently ‘tonic’ dystonia [8]. Our observation does not support this hypothesis: despite the fact that about half of our patients had ‘phasic’ movements, equal improvement on ‘tonic’ postures and ‘phasic’ dystonic movements was observed.

Speech and swallowing were improved, as shown by the BFMDRS motor and functional subscores (Table 2). This expands an earlier multicenter 1-year observation [8] and a small series with a 2-year outlook [5]. The parallel improvement of both motor and functional subscores is of particular note, as speech and swallowing impairment is often observed in DCP patients. Another point of analysis is the finding that

**Table 3** Adverse events and side effects in the whole series

| Events                                                          | Type of event (no. of occurrences)                                                                    |
|-----------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Transient                                                       | Fever (2), seizure (1), spasms of pharynx (1)                                                         |
| Persistent                                                      | Dysphagia and hypophonia (1), hypophonia (1)                                                          |
| Stimulation-induced                                             | Dysarthria (4), local pain (2), paresthesia (2), muscular strain (1), visual disturbance (1)          |
| Occurring during surgical procedures                            | Extracranial lead damage (1), subclavicular seroma (1)                                                |
| Device-related                                                  | Unexplained implantable pulse generator switching-off (1), lead migration (1), hardware infection (1) |
| Unrelated to the surgical procedure or stimulation              | Death for acute cardiac failure (1)                                                                   |
| Total number of adverse events and side effects/no. of patients | 25/15                                                                                                 |

Adverse events were classified as transient, persistent (if not improved by turning off stimulation for a short time), stimulation-induced (present at optimal stimulation parameters but improved when stimulation was turned off or stimulation parameters were modified), device-related, or unrelated to the procedure or stimulation.

mild static MRI abnormalities do not negatively influence outcome. Two patients are reported here with DCP secondary to kernicterus, one of whom had slight basal ganglia (mainly pallidal) MRI changes and improved significantly after implant. This observation is in keeping with an earlier report on similar patients who received GPi implants [7] and suggests that a clinical trial specifically dedicated to this type of patient is warranted. Similarly, no differences in outcome for patients with or without mild spasticity were found. Although it cannot be ruled out that medication changes may have caused some improvement in spasticity, it is remarkable that most patients had a stable or reduced medical regimen after implant.

It is also confirmed that outcome is to some extent heterogeneous, with some patients improving less than others. Patient 5, who had no benefit, was found to have incorrect location of the therapeutic contacts in the left electrode, with a stimulated volume area located outside the GPi boundaries (Fig. S2). This underlines the crucial importance of a correct lead placement to obtain optimal outcomes [8]. In addition, patients 13 and 14 had a remarkable initial motor and functional improvement that partially relapsed after 2 years, without an identifiable cause; these patients, however, still retained an appreciable improvement at last follow-up (6 years).

Energy consumption is a concern in patients with dystonia who receive GPi implants. In this series, only minor modifications of stimulation settings were performed after the second year post-implant, mainly consisting in an increase of amplitude or pulse duration (Fig. 1). There are no comparable data for DCP and this finding is in keeping with observations in idiopathic or inherited dystonias [2]. An average battery life of about 56 months was observed, similar to that reported for subthalamic DBS in Parkinson disease

[21] and substantially longer than in other studies reporting an average battery life of about 24.5 months in adult patients with segmental or generalized dystonia [22], in children with acquired dystonia [23] and in a population with generalized idiopathic or inherited dystonia [19]. Compared with these studies, a lower stimulation frequency was used and a shorter pulse duration once settings were stabilized, leading to a lower battery current drain. Our experience supports the view that energy delivery does not need to be unnecessarily high to provide a clinical improvement in dystonia [19, 24].

Disability, quality of life and pain improved in the majority of patients, albeit unevenly, permitting in several cases acceptable personal autonomy to be recovered and social functioning to be improved. The body pain score was particularly improved and paralleled the reduction in dystonia severity. Globally, these findings are in keeping with previous observations on pediatric [7] and adult DCP patients [8]. Cognitive and psychiatric safety is in keeping with earlier reports on adult DCP patients [8]. The overall safety outlook of this series is encouraging with a global burden of complications slightly higher than previously reported [25].

Although experience is accumulating on the efficacy and safety of DBS in DCP, longer-term (5–10 years) dedicated trials with large patient populations are warranted to further refine the clinical understanding of this important indication. The outcome and safety issues highlighted here indicate an interesting potential for this treatment and pave the way for a post-implant management strategy in DCP patients.

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### Disclosure of conflicts of interest

Luigi M. Romito received speaker's honoraria from Medtronic. Alberto Albanese serves on the editorial board of the *European Journal of Neurology* (Associate Editor) and *Frontiers in Movement Disorders* (Editor in Chief) and received speaker's honoraria from TEVA, Allergan, Merz, Ipsen and Medtronic. He also received royalties from publishing from Elsevier, Wiley-Blackwell. The other authors declare no financial or other conflicts of interest.

### Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Brain MRI scans of patient 7 illustrates mild abnormalities in the basal ganglia secondary to

kernicterus (arrows). (A) Proton density weighted MRI; (B) T2-weighted MRI.

**Figure S2.** Reconstruction of electrode positioning and volume of tissue activated by the electrical field around them in each patient. In an anterior view of the brain stem the GPi (green), the ansa lenticularis (purple) and optic tract (blue) are individually reconstructed in three dimensions. The electrode location and the volume of tissue activated are superimposed on the anatomical landmarks (images generated by the Optimise DBS care Management Software). Numbers refer to each patient's ID, as reported in Table 1. It is of note that patient 5 had incorrect location of the therapeutic contacts in the left electrode, with a stimulated volume area located outside the GPi boundaries. L, left; R, right.

**Table S1.** Demographic and clinical features of individual patients of the series.

**Table S2.** Health-related quality of life subscores (SF-36) before and after DBS.

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