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Chronic bilateral pallidal stimulation in patients with generalized primary dystonia – multi-contact cathodal stimulation is superior to bipolar stimulation mode. Preliminary results

Przewlekła obustronna stymulacja części wewnętrznych gałek bladych u chorych z dystonią uogólnioną – wielokontaktowa katodalna stymulacja jest skuteczniejsza niż stymulacja bipolarna. Wyniki wstępne

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Abstract

Background and purpose: Primary generalized dystonia (PGD) is a medically refractory progressive disease of the brain causing near total handicap of affected patients. The aim of the study was to assess the efficacy and safety of bilateral pallidal stimulation in patients with PGD.
Material and methods: The study population is composed of 5 patients with PGD. The formal objective assessment included the Burke-Fahn-Marsden dystonia rating scale (BFMDRS). All stereotactic procedures were performed in general anaesthesia using a Leksell G stereotactic head frame without electrophysiological guidance. Immediately after insertion of deep brain stimulation (DBS) leads, the internal pulse generators (Itrel II or Soletra) were implanted subcutaneously in the chest wall or abdominal region.
Results: There were no complications related to the stereotactic procedures. The hardware-related complications (two broken DBS leads) were replaced successfully. There were no infections or erosions of implanted hardware. It has been observed that in the long-term follow-up period primary set bipolar stimulation mode lost its benefit achieved previously. Various stimulation combinations were investigated. Mono-

Streszczenie

Wstęp i cel pracy: Pierwotna dystonia uogólniona to postępujące, oporne na leczenie farmakologiczne schorzenie, które prowadzi do prawie całkowitego inwalidztwa dotkniętych nim chorych. Celem tej pracy jest ocena skuteczności i bezpieczeństwa obustronnej stymulacji części wewnętrznych gałek bladych u chorych z pierwotną dystonią uogólnioną.
Materiał i metody: Badaną grupę stanowiło 5 pacjentów. Stopień nasilenia dystonii oceniono obiektywnie w skali *Burke-Fahn-Marsden Dystonia Rating Scale* (BFMDRS). Wszystkie operacje stereotaktyczne przeprowadzono w znieczuleniu ogólnym z wykorzystaniem ramy stereotaktycznej Leksell G bez śródoperacyjnego badania elektrofizjologicznego. Bezpośrednio po wszczepieniu elektrod do głębokiej stymulacji mózgu, generatory impulsów (Itrel II lub Soletra) wszczepiono podskórnie w okolice klatki piersiowej lub powłoki jamy brzusznej.
Wyniki: Nie obserwowano powikłań związanych z operacjami stereotaktycznymi. Dwie uszkodzone – przerwane – elektrody do głębokiej stymulacji mózgu wymieniono bez powikłań. Nie stwierdzono zakażeń ani nadżerek wszczepionych elementów do głębokiej stymulacji mózgu. W obserwacji pooperacyjnej zauważono, że stymulacja bipolarna zaczęła tracić swój

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polar cathodal or especially multi-contact cathodal stimulation was the most effective one. The efficacy of bilateral pallidal stimulation was proved by the objective validated BFMDRS at long-term follow-up.

Conclusions: Response to DBS may improve with the number of activated cathodal contacts within the globus pallidus internus.

Key words: generalized primary dystonia, bilateral pallidal stimulation, deep brain stimulation, neuromodulation.

korzystny efekt widoczny w bezpośrednim okresie pooperacyjnym. U chorych próbowano zastosować różne kombinacje aktywnych kontaktów wszczepionych elektrod. Okazało się, że najskuteczniejsza jest stymulacja katodalna, a szczególnie wielokontaktowa stymulacja katodalna. Skuteczność stymulacji katodalnej potwierdzono w obserwacji długoterminowej na podstawie skali BFMDRS.

Wnioski: Skuteczność głębokiej stymulacji mózgu może się zwiększać wraz z liczbą aktywnych kontaktów jako katody w zakresie części wewnętrznej gałki bladej.

Słowa kluczowe: pierwotna dystonia uogólniona, obustronna stymulacja gałek bladych, głęboka stymulacja mózgu, neuromodulacja.

Introduction

Primary generalized dystonia (PGD) is a medically refractory progressive disease of the brain causing near total handicap of affected patients. PGD is defined as dystonia being the sole clinical manifestation attributable to the condition with no evidence of imaging, laboratory, or pathological abnormalities [1,2]. As novel gene mutations are recognized, dystonias of previously unknown origin have been demonstrated to have a genetic basis. To date, 15 genetic loci associated with dystonias have been identified.

The pharmacological treatment options for patients with PGD are limited. In most cases, pharmacotherapy of patients with PGD fails to adequately alleviate symptoms. Moreover, pharmacotherapy is not curative.

Surgical treatment options for patients with PGD have evolved as a result of inadequate achievements of medical therapy [1,2]. Selective peripheral denervation has been performed for botulinum toxin resistant cases of focal cervical dystonia [3,4]. This type of surgery is not suitable in cases of PGD. Thalamotomy has been associated with adequate but inconsistent results, as well as complications [5]. The incidence of complications, particularly dysphagia and dysarthria, increases when thalamotomy is performed bilaterally [5,6]. The second most common ablative procedure – pallidotomy – effectively diminishes levodopa-induced dyskinesia and off-period early morning dystonia in Parkinson disease patients. Case reports support the observation that pallidotomy may be beneficial not only in Parkinson disease patients with dystonic features but also in patients with PGD [7,8]. Some patients gained great functional benefit in long-term follow-up after bilateral staged or even simultaneous bilateral pallidotomy [9-11]. These observations have lent further support to the role of the internal part of the globus pallidus (GPi) as a target for neuromodulation in dystonia surgery [12-14]. The preliminary results of bilateral pallidal stimulation in patients with PGD associated with DYT-1 mutation were very encouraging [12,13]. Adjustability of stimulating parameters, reversibility of stimulation, and feasibility of bilateral electrode implantation without adverse effects make pallidal stimulation an attractive surgical alternative for the treatment of patients with PGD [12,13,15]. The GPi is an established target especially in PGD patients with DYT-1 mutation, but also in patients without DYT-1 mutation.

There are no conclusive data regarding the best parameters of stimulation and stimulation mode in the postoperative period. Various authors use different stimulation parameters including pulse width, frequency and voltage in the postoperative period [12,15-17]. Also, different groups use divergent stimulation modes – bipolar or multicontact cathodal [13-19,21]. In subthalamic nucleus surgery for Parkinson disease, the most efficient stimulation mode is monopolar cathodal. The parameters are set initially at 60 μs, 130 Hz, and voltage is steadily increased. An improvement in Parkinson disease symptoms is usually seen immediately after switching on the stimulation. A different situation exists in dystonia patients. Improvement in dystonic features is achieved after a period of 2 or even 6 months after surgery, but not immediately. Initial parameters for pallidal stimulation require a longer pulse width, usually 210 μs or even longer, up to 450 μs [14-21]. Most authors use a stimulation frequency above 130 Hz in patients with PGD [12-17,20,21]. The stimulation mode varies greatly between authors [12-15,18-21]. It is usually bipolar, using the most distal

contact as the cathode and the most proximal as the anode [15,17-19]. Other authors use the monopolar cathodal stimulation mode [20]. For a pallidal target, longer DBS leads (model 3387, Medtronic, Minneapolis) are implanted. In some patients, dystonic features deteriorate over time even under chronic bilateral pallidal stimulation. This has led to further investigation of various stimulation parameters and contacts of implanted leads to achieve maximal clinical benefit. Some authors implant a second deep brain stimulation lead to influence a larger volume of somatosensory territory of the GPi [21].

Like other groups, we initially used the bipolar stimulation mode in PGD patients, using the most distal contact as the cathode and the proximal contact as the anode. The stimulation parameters were set at 210 μs, 130 Hz, with increasing voltage. We achieved benefit in most PGD patients according to Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) scores in the early postoperative period. These functional and motor improvements were lost in further follow-up while simultaneously increasing the voltage. Changing the stimulation mode from the initially set bipolar to monopolar or multicontact cathodal proved efficient in alleviating dystonia. The aim of this study was to discuss the results and the regained benefit using multicontact cathodal stimulation in patients with PGD.

Material and methods

The study population comprised our 5 first patients with diagnosis of PGD with at least 2 years follow-up. The patients included in the study were operated on at the Neurosurgical Department of the Postgraduate Medical Centre in Warsaw between November 2001 and December 2007. Only patients with a completed two-year follow-up operated on in this period were included and discussed in the present study. All patients were informed about stereotactic procedures and signed informed written consent. The ethical committee of the Postgraduate Medical Centre in Warsaw approved the study protocol. All patients underwent the same stereotactic procedure using a Leksell stereotactic G Frame and the same clinical assessment before and after surgery. Pharmacological therapy failed to achieve substantial improvement in these patients.

Before surgery all patients underwent screening for detection of DYT-1 mutation. Two patients were diagnosed positive for DYT-1 mutation, and the remaining three were negative for DYT-1 mutation. The clinical characteristics of the patients with DYT-1 mutation and without DYT-1 are shown in Table 1. All patients referred for surgical treatment were assessed according to the BFMDRS before surgery and at follow-up visits. The follow-up examinations according to the BFMDRS were performed at regular visits at 6 months and thereafter annually. The postoperative BFMDRS scores in stimulation on condition were compared to the preoperative BFMDRS scores to assess the effects of stimulation on dystonia in various body parts according to the Burke-Fahn-Marsden dystonia rating scale (BFMDRS). All patients were operated on under general anaesthesia because of severe dystonia and young age. Following attachment of the Leksell type G stereotactic head frame (Leksell Elekta, Stockholm, Sweden) under general anaesthesia, the stereotactic computed tomography (CT) images were done. These CT images were merged with magnetic resonance images (MRI) using a surgical planning software package (Framelink 4.1, Stealth Station, Medtronic Minneapolis, MN). The posteroventral pallidum was selected using the coordinates chosen for posteroventral pallidotomy, which were usually 20-21 mm lateral, 2-3 mm anterior and 4-5 mm inferior to the midcommissural point. The chosen stereotactic target point was carefully evaluated and changed if needed in every case. The entry points were selected and the trajectories to the stereotactic targets were

Table 1. Patient characteristics

Patients	DYT-1 mutation presence	Sex	Age at onset [years]	Duration of disease [years]	Last follow-up visit [years]
Patient 1	+	male	7	17	7
Patient 2	+	male	12	9	3
Patient 3	-	male	11	8	3
Patient 4	-	female	15	7	2
Patient 5	-	male	19	10	2

traced bilaterally using coronal, parasagittal, and axial MRI images. Special attention was paid to avoid transversing the sulci, lateral ventricle, and cortical veins. After imaging, the patient was placed in a comfortable semisitting position on the operating table. The burr holes were placed according to the entry points selected during trajectory planning. The burr holes were usually made 3 to 4 cm from the midline and 1 cm before the coronal suture or at the coronal suture. The burr holes were located at the uppermost point which effectively prevented pneumocephalus during stereotactic procedures and excessive cerebrospinal fluid leakage. The burr holes were made simultaneously. We usually operated on the right hemisphere first. After implantation of one DBS lead, the dura mater of the opposite hemisphere was coagulated and incised. Moreover, after opening of the dura mater, the operating field was irrigated with saline, which also prevented the entry of air into the cranial vault. The proper depth of DBS leads implantation was checked by lateral fluoroscopic monitoring. The DBS leads were implanted in such a way that contact 0 was set to be at stereotactic target. After fixation of the DBS leads at the burr holes using a Medtronic burr hole cap, another lateral X-ray was performed to check the final position of the DBS leads. All patients tolerated the stereotactic procedures without complications.

After implantation of DBS leads, the internal pulse generators (IPG), Itrel II or Soletra (Medtronic, Inc., Minneapolis, MN), were placed in the subclavicular region of the chest wall or abdominal wall and connected to the DBS leads on the same day. Postoperative CT was done immediately after surgery to exclude any haemorrhage. The sutures were removed on the 8th postoperative day. At that time, the patients were discharged home.

The day after implantation of DBS hardware, the impedance of implanted DBS contacts was checked. In the monopolar cathodal stimulation mode, the DBS leads were evaluated to watch for stimulation-induced side effects. Thereafter, the stimulation parameters were set for continuous bilateral stimulation (with steadily increasing voltage of 1.0 to 3.9 V; pulse rate 130 Hz; and pulse width 210 μs). In all implanted DBS leads, the lowest contacts (contacts 0 or contact 1) were chosen as the cathode and the uppermost contacts (contacts 3) were chosen as the anode. The stimulation mode was bilateral bipolar continuous.

Results

The patients were evaluated with BFMDRS before and after surgery. The patients were assessed in the follow-up period in stimulation *on* condition. The postoperative BFMDRS scores in the *on* condition were compared to the preoperative BFMDRS scores. The BFMDRS scores were evaluated separately for patients with DYT-1 positive and for patients with DYT-1 negative PGD. The preoperative and postoperative BFMDRS scores for individual patients with DYT-1 positive and negative PGD are shown in Table 2. The mean preoperative motor score for patients with DYT-1 positive PGD was 88.5, and at the last follow-up visit it was 28. The mean preoperative disability score for patients with DYT-1 dystonia was 17.5 and it dropped to 7 at the last postoperative follow-up visit. At the last follow-up visit in 2 patients with DYT-1 positive PGD, the functional and motor parts of the BFMDRS were improved by 60% and 68%, respectively, when compared to the preoperative scores (Table 2). The mean preoperative motor score for patients with DYT-1 negative PGD was 44 and at the last postoperative visit it was 26. The mean preoperative disability score for patients with DYT-1 negative PGD was 10 and it was 5 at the last follow-up visit. In 3 patients with DYT-1 negative PGD the functional and motor parts of the BFMDRS improved by 50% and 41%, respectively, when compared to the preoperative BFMDRS scores (Table 2).

The stimulation mode was not usually changed over the follow-up period until the second postoperative year. In 5 patients (2 with DYT-1 positive PGD, and 3 patients with DYT-1 negative PGD) dystonic movements reappeared although the voltage was steadily increased in bipolar mode. In 1 patient with DYT-1 positive PGD, the symptoms were controlled under bilateral bipolar stimulation mode over the entire follow-up period. In this patient switching from bilateral to monopolar stimulation mode resulted in corticobulbar effects that forced us to stimulate this patient only using the bipolar stimulating mode (patient no. 1).

In the remaining 4 patients with deterioration of symptoms usually seen in the second postoperative year we switched from bipolar to monopolar cathodal stimulation mode. We switched stimulation mode from bipolar to monopolar in patient 2 after 13 months, in patient 3 after 15 months, in patient 4 after 8 months and in patient 5 after 18 months of continuous bipolar stimulation mode. When switching from bipolar to monopolar stimulation mode we were forced to reloca-

Table 2. Preoperative and postoperative BFMDRS scores in patients with DYT-1 positive and negative dystonia

Patients		Preoperative BFMDRS scores	Postoperative scores using bipolar stimulation mode	Postoperative scores using monopolar stimulation mode	Interval between surgery and switching from initial bipolar to monopolar stimulation mode
Patients with DYT-1 positive dystonia					
	Patient 1	FS = 24 MS = 112	FS = 7 MS = 28	Only bipolar stimulation mode FS = 9 MS = 30	Only bipolar mode due to corticobulbar activation
	Patient 2	FS = 11 MS = 65	FS = 9 MS = 44	FS = 5 MS = 26	13 months
Patients with DYT-1 negative dystonia					
	Patient 3	FS = 13 MS = 53	FS = 10 MS = 41	FS = 7 MS = 30	15 months
	Patient 4	FS = 8 MS = 34	FS = 7 MS = 29	FS = 3 MS = 20	8 months
	Patient 5	FS = 9 MS = 45	FS = 7 MS = 32	FS = 5 MS = 28	18 months

BFMDRS – Burke-Fahn-Marsden Dystonia Rating Scale, FS – functional scores (range 0-30), MS – motor scores (range 0-120)

te the active contacts because most patients experienced phosphenes or mouth corner twitches, and upper limb twitches when using the lowest contacts (contacts 0-1) as cathodes. These stimulation-induced side effects were still present even though the stimulation voltage was significantly decreased. The use of two middle or two upper contacts decreased these stimulation-related side effects. In some patients we added an additional contact as the cathode in the third postoperative year.

The stimulation parameters in individual patients are presented in Table 3. The stimulation mode and active contacts of implanted DBS leads in individual patients are presented in Table 4. During the follow-up period, hardware-related complications occurred in 2 patients (2 breakages of DBS leads). One breakage was located in proximity to the burr hole cap and one just above the connector. All breakages were attributable to slippage of the connector and increased tension exerted on the extracranial part of the DBS lead. All broken DBS leads were exchanged under general anaesthesia in stereotactic conditions. The connectors were placed in parietal regions as previously but additionally sutured to the galeal fascia to prevent further slippage. The further postoperative course of these 2 patients was uneventful. We noted no additional hardware-related complications. There were no erosions or infections of implanted hardware. Two patients required in the follow-up period IPG replacement because of battery depletion. One patient developed sterile seromas at the IPG sites. The seromas required repeated procedures. We noted no other complications associated with implanted hardware.

Discussion

Our results confirm the efficacy of bilateral pallidal stimulation in patients with PGD. The functional and motor improvements are maintained at 2 years using validated BFMDRS scores. Other authors have also confirmed the clinical efficacy of bilateral pallidal stimulation with two-year or even longer follow-up [18-20]. Our study group included only patients with PGD. We did not include patients with other forms of dystonia. All patients before surgery underwent screening for DYT-1 mutation. The presence of DYT-1 mutation is thought to be a good predictor for a good postoperative response to pallidal stimulation. Some authors have achieved near total disappearance of PGD symptoms, especially in this group. The mean postoperative improvements regarding disability and motor

Table 3. Stimulation parameters in patients with DYT-1 positive and negative primary generalized dystonia using bipolar and monopolar stimulation mode

Patients with primary generalized dystonia	Neurostimulation parameters using bipolar stimulation mode		Neurostimulation parameters using monopolar stimulation mode	
Stimulation side (cerebral hemisphere)	**Right**	**Left**	**Right**	**Left**
Patient 1				
Frequency	130 Hz	130 Hz	130 Hz	145 Hz
Pulse width	210 μs	210 μs	210 μs	210 μs
Voltage	2.2 V	2.5 V	2.5 V	2.5
Patient 2				
Frequency	130 Hz	130 Hz	145 Hz	145 Hz
Pulse width	210 μs	210 μs	210 μs	210 μs
Voltage	3.1 V	3.7 V	2.3 V	2.8 V
Patient 3				
Frequency	130 Hz	130 Hz	145 Hz	130 Hz
Pulse width	210 μs	210 μs	210 μs	210 μs
Voltage	2.9 V	3.3 V	2.4 V	2.8 V
Patient 4				
Frequency	130 Hz	130 Hz	145 Hz	130 Hz
Pulse width	210 μs	210 μs	210 μs	210 μs
Voltage	3.8 V	3.2 V	2.6 V	2.7 V
Patient 5				
Frequency	130 Hz	130 Hz	145 Hz	130 Hz
Pulse width	210 μs	210 μs	210 μs	210 μs
Voltage	3.9 V	3.6 V	2.8 V	2.5 V

Table 4. Stimulation mode and active contacts used in patients with positive and negative primary generalized dystonia

Patients with primary generalized dystonia	Stimulated contacts using bipolar (anodal-cathodal) stimulation mode		Stimulated contacts using monopolar (cathodal) stimulation mode	
Stimulation side (cerebral hemisphere)	**Right**	**Left**	**Right**	**Left**
Patient 1	Bipolar contact 0 (–) contact 3 (+)	Bipolar contact 0 (–) contact 3 (+)	Bipolar contact 1 (–) contact 3 (+)	Bipolar contact 0 (–) contact 3 (+)
Patient 2	Bipolar contact 0 (–) contact 2 (+)	Bipolar contact 0 (–) contact 3 (+)	Monopolar contact 2 (–) contact 3 (–) case (+)	Monopolar contact 1 (–) contact 2 (–) contact 3 (–) case (+)
Patient 3	Bipolar contact 0 (–) contact 3 (+)	Bipolar contact 1 (–) contact 3 (+)	Monopolar contact 1 (–) contact 2 (–) case (+)	Monopolar contact 1 (–) contact 2 (–) case (+)
Patient 4	Bipolar contact 1 (–) contact 3 (+)	Bipolar contact 0 (–) contact 2 (+)	Monopolar contact 2 (–) contact 3 (–) case (+)	Monopolar contact 1 (–) contact 2 (–) case (+)
Patient 5	Bipolar contact 1 (–) contact 3 (+)	Bipolar contact 0 (–) contact 2 (+)	Monopolar contact 2 (–) contact 3 (–) case (+)	Monopolar contact 1 (–) contact 2 (–) case (+)

BFMDRS scores in patients with DYT positive PGD were 60% and 68%, respectively. In PGD patients negative for DYT-1 mutation, the postoperative course is less predictable. The remaining 3 patients with DYT-1 negative PGD also gained functional and motor benefit slightly less evident than patients positive for DYT-1 mutation. The functional and motor BFMDRS score improvements were 50% and 41%, respectively. Regardless of the presence of DYT-1 mutation in patients with treatment-refractory PGD the surgical approach should be considered as a valuable treatment modality.

The initial stimulation mode used in our patients was bipolar. We noted clinical deterioration in some patients although the pulse width and voltage were steadily increased. This observation forced us to change the stimulating mode from bipolar to multicontact cathodal. This observation can be explained by progression of PGD symptoms even under continuous bilateral pallidal stimulation. The mean age of our patients was lower than the reported mean age of patients treated by other authors [16-18]. This can explain faster natural progression of PGD and also worsening of symptoms even under bilateral pallidal stimulation. Some authors report that the age at the onset of symptoms is a predictive factor of natural progression of PGD. In adolescent and adult patients, progression of PGD symptoms is slower than in children.

Although increasing the voltage or the number of activated contacts within the GPi will not always provide additional benefit in patients who initially responded favourably to pallidal stimulation, some authors tried to implant a second DBS lead to achieve additional improvement [20].

The reversibility of the DBS procedure creates the possibility to investigate various stimulation parameters in the follow-up period. Effort should be made to minimize differences including surgical protocols, used DBS lead types, and stimulation parameters. This could help to provide preliminary stimulation parameters which would bring the greatest benefit to patients.

The management of patients with PGD is very challenging. The results of pharmacological treatment are often disappointing. Bilateral pallidal stimulation can decrease the patient's disability and improve the functional status of patients. Although the initial response to pallidal stimulation is satisfactory in PGD patients, the improvement diminishes over the follow-up period. This could be explained by the fact that DBS is only symptomatic treatment for these patients and is not able to halt disease progression. Nevertheless, bilateral pallidal stimulation is the most efficient symptomatic treatment modality for PGD patients.

Conclusions

1. Chronic bilateral pallidal stimulation is an effective and safe treatment in patients with PGD.
2. The efficacy of bilateral pallidal stimulation was proved by the objective validated BFMDRS at least 2 years postoperatively.
3. Response to deep brain stimulation may improve with the number of activated contacts as cathodes within the internal part of the globus pallidus.

Disclosure

Authors report no conflict of interest.

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