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Short communication

Bilateral pallidal stimulation for sargoglycan epsilon negative myoclonus☆

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ABSTRACT

We report on the clinical efficacy of bilateral globus pallidus internus deep brain stimulation in two patients with myoclonus dystonia/essential myoclonus who lack mutations in the epsilon sarcoglycan gene.

The primary outcome measures were the Burke–Fahn–Marsden Dystonia Scale motor severity and the Unified Myoclonus Rating Scale scores, and the secondary outcome measure was the 36-item Short Form Health Survey score at the last postoperative follow up. Neuronal firing rates were also calculated from microelectrode recordings.

At the last postoperative follow-up (16 weeks for Patient 1 and 18 weeks for Patient 2), there was 57.1% (Patient 1) improvement in the Burke–Fahn–Marsden Dystonia Scale motor severity score and 31.3% (Patient 1) and 69% (Patient 2) in the Unified Myoclonus Rating Scale score while individual SF-36 scores showed improvement in most subdomains.

Bilateral globus pallidus internus deep brain stimulation can be effective in ameliorating epsilon sarcoglycan negative myoclonus with or without concurrent dystonia. Whether an epsilon sarcoglycan negative status represents a less favorable prognostic factor for pallidal deep brain stimulation remains to be elucidated.

1. Introduction

Myoclonus is an etiologically and phenotypically heterogeneous syndrome not uncommonly accompanied by dystonia. Myoclonus dystonia (MD) is one of the more common causes of this combination. The most common defined cause of MD is a mutation in the epsilon sarcoglycan gene (SGCE), (OMIM 604149) on chromosome 7q21, also known as DYT 11. The term DYT 15 (OMIM 607488) is associated with the locus 18p11, although the gene has not been yet identified [1]. It is now recognized that MD is a genetically but also phenotypically heterogeneous disorder characterized by myoclonic jerks affecting mostly proximal muscles. Dystonia, when present, usually manifests as torticollis or writer's cramp, but occasionally can be the only symptom. Pharmacotherapy can provide some symptom relief, however treatment resistance and poor patient tolerance are common. Globus pallidus internus deep brain stimulation (GPi DBS) is a well-established treatment for primary and secondary dystonias with satisfactory long-term outcomes [2-4]. In the last decade, several case reports and two small studies have evaluated the benefits of GPi DBS [5,6], ventral intermediate (Vim) thalamic nucleus DBS [7] or a combination of the two [8] in ameliorating symptoms of MD patients with promising results. Vim

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DBS [9] and GPi DBS [10] have also been used in secondary forms of isolated myoclonus with encouraging results. We report the short term outcomes of two SGCE (−) patients, one with an MD phenotype and another with a phenotype of isolated myoclonus, who underwent bilateral GPi DBS in our center. Moderate improvements in myoclonus and dystonia were seen. Myoclonus improved less than in other previously reported studies and this could potentially be attributed to the SGCE (−) status.

2. Patient 1

The first patient is a 14 year old boy initially symptomatic at the age of 2½ years when he developed hand, neck and arm jerks. Moreover, he exhibited excessive eye blinking which was suspected to represent a tic without any convincing evidence of other phonic or motor tics. At the age of five, he developed mild bilateral arm dystonia. Symptoms were refractory to antitremor and antimyoclonic pharmacotherapy, including levodopa. Genetic testing was negative for SCGE mutations. He is a member of the single family reported with the DYT 15 form of MD, however, he represented the one exception for linkage to the DYT 15 locus on chromosome18p11 [1]. Apart from the patient's myoclonus and truncal and appendicular dystonia (Video Segment 1), his general neurological exam was unremarkable. He exhibited mild obsessive-compulsive symptoms manifested as aligning books and organizing toy blocks in specific patterns. Neuroimaging was normal. Due to refractory symptoms, clearly interfering with activities of daily living, and the lack of alternative treatment modalities, the decision was made to proceed with DBS.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.04.017

3. Patient 2

Patient 2 is a 49 year old woman, initially symptomatic at the age of 15 when she developed hand jerks with a significant response to alcohol, which lead to periods of alcohol dependence. During her follow-up of 15 years at our center, trials of antimyoclonic medications such as clonazepam and lorazepam partially controlled her myoclonus but at the cost of unacceptable sedation. There was no family history of myoclonic jerks or dystonia.

On clinical examination she exhibited moderate rest, postural and action myoclonus in the arms that would interfere significantly with manual tasks such as handwriting (Video Segment 2). The rest of her neurological examination was unremarkable. Brain MRI was normal. Genetic testing was also negative for SCGE mutations. Due to conservative treatment resistant symptoms the decision was made to proceed with DBS.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2014.04.017

4. Outcomes

The primary outcome measures were the Burke-Fahn-Marsden Dystonia Scale motor severity (BFMDS-M) and the Unified Myoclonus Rating Scale (UMRS) (Items 2–5) scores. For the BFMDS-M, videotapes were obtained at baseline, at six weeks postoperatively and at the last follow-up (16 weeks for Patient 1 and 18 weeks for Patient 2). The video protocol for the UMRS was not available before DBS, so the baseline assessment was considered at 6 weeks postoperatively, after complete resolution of the initial microlesioning effect, as reported by the patients, and before DBS programming was initiated. All videotapes were randomized and scored blindly by a single movement disorders neurologist (T.M). The secondary outcome measures were the components of the Short Form 36 Health Survey (SF-36) at baseline and at last follow up.

5. Surgical procedure

Bilateral GPi DBS was performed under general anesthesia for Patient 1 and under local anesthesia for Patient 2 using routine stereotactic methods and microelectrode recordings as described elsewhere [11]. Template matching and peristimulus time histogram algorithms built into Spike 2 software (Cambridge Electronic Design [CED], Cambridge, UK) were used for cell discrimination and calculation of firing rates. A single electrode trajectory was used for all four GPi targets. Postoperative MRI confirmed appropriate lead positioning in the GPi (Fig. 1).

6. Postoperative stimulation parameters

Approximately 6 weeks after surgery and once the microlesion effect had completely resolved, both patients underwent initial programming with subsequent repeated evaluations for optimization of electrical stimulation parameters. At the last post-operative follow up stimulation settings were as follows: Patient 1: right GPi C + 2-, 3 V/60 μs/130 Hz, left GPi C + 10-, 3 V/60 μs/130 Hz. Patient 2: right GPi C + 2-3-, 2.7 V/90 μs/125 Hz, left GPi with interleaving stimulation, in a bipolar mode, 11 + 10- 2 V/90 μs/125 Hz, 11+9- 2.7 V/60 μs/125 Hz.

7. Results

7.1. Patient 1

7.1.1. Intraoperative recording

A total of 34 GPi neurons were analyzed. The mean neuronal firing rate was 16.9 ± 14.7 Hz.

7.1.2. Clinical assessment

Blinded baseline BFMDS-M score was 10.5/120 (higher numbers indicating greater severity of dystonia) and UMRS score was 112/325 (Items 2–5 of the UMRS) (higher numbers denoting greater myoclonus). 16-week postoperative scores were 4.5/120 and 77/325 indicating a 57.1% and 31.3% improvement respectively (Video segment 3). Programming was challenging as the initial thresholds for side effects in a monopolar mode (leg paresthesias) were in the range of 1.8–2.5 V for all contacts whereas the use of a bipolar mode did not provide any sustained motor improvement. When side effects in a monopolar setting were re-explored approximately 10 weeks postoperatively, they were found to be on average 0.5 V higher at each contact compared to the initial evaluation. Baseline and 16-week post-operative SF-36 scores are provided in Table 1.

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7.2. Patient 2

7.2.1. Intraoperative recording

A total of 26 GPi neurons were analyzed. The mean neuronal firing rate was 53.1 ± 10.6 Hz.

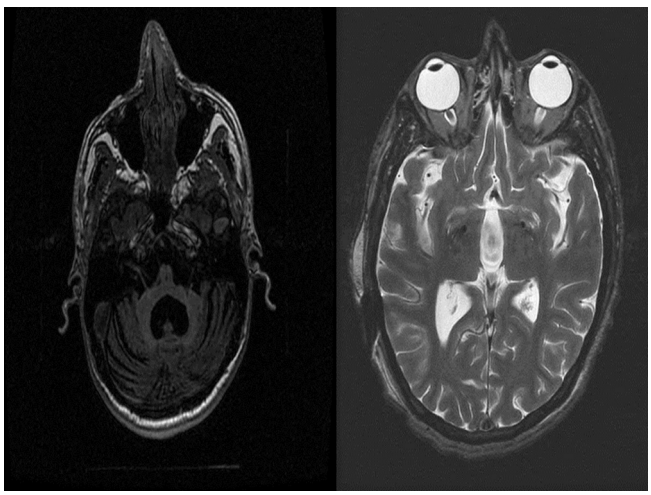

Fig. 1. T2-weighted axial postoperative MRI scans, verifying appropriate lead positioning, Patient 1 (Left), Patient 2 (Right).

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