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Review

Early deep brain stimulation in patients with myoclonus-dystonia syndrome

Helena Rocha [a,b,*], Paulo Linhares [b,c,d], Clara Chamadoira [b,c,d], Maria José Rosas [a,d], Rui Vaz [b,c,d]

[a] Department of Neurology, Centro Hospitalar São João, Porto, Portugal
[b] Department of Clinical Neuroscience and Mental Health, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal
[c] Department of Neurosurgery, Centro Hospitalar São João, Porto, Portugal
[d] Movement Disorders and Functional Surgery Unit, Centro Hospitalar São João, Porto, Portugal

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ABSTRACT

Myoclonus-dystonia (MD) is a rare movement disorder which is disabling and frequently refractory to medical treatment. Deep brain stimulation (DBS) of the globus pallidus interna (GPi) has been used to treat some patients. Although there is significant motor improvement with DBS, the impact on disability and on quality of life has been infrequently reported. Also, the benefit of the procedure is not established in patients without ε-sarcoglycan gene (*SGCE*) mutations. We present two patients with severe MD treated with GPi-DBS, one of the patients without a *SGCE* mutation. Motor improvements (rest/action/total subscores of the Unified Myoclonus Rating Scale and movement subscore of the Burke-Fahn-Marsden Dystonia Rating Scale [BFMRS]) and disability (BFMRS disability subscore) were carefully evaluated preoperatively and at 6 and 12 months after surgery. Quality of life (addressed using the Portuguese version of the Medical Outcomes Study 36-item Short-Form General Health Survey, version 2.0 [SF-36v2]) was tested preoperatively and 12 months after DBS. At 12-month follow-up, myoclonus improved 78.6% in Patient 1 and 80.7% in Patient 2, while dystonia improved 37% and 86.7%, respectively. Improvements in disability ranged from 71.4% to 75%. With regard to quality of life, all parameters addressed by the SF-36v2 improved or stabilized in both patients. No major adverse effects were noticed. Improvements in motor symptoms are consistent with reports in the literature and were obtained regardless of the identification of a *SGCE* gene mutation. There were also significant benefits on disability and quality of life. DBS should be considered for MD.

1. Introduction

Myoclonus-dystonia (MD) is a rare combined persistent dystonia syndrome where both myoclonus and dystonia are present with variable degrees of severity and disability. It typically begins during childhood or adolescence [1–3]. Positive myoclonus, the most prominent and disabling feature, mainly affects the proximal upper limbs and axial musculature. It is triggered by action or emotional stress and is alcohol-responsive [1,4]. Dystonia, on the other hand, is often mild, with cervical dystonia or writer's cramp the most common manifestations [4].

The disease has an autosomal dominant inheritance pattern due to a pathogenic mutation in the ε-sarcoglycan gene (*SGCE*) – DYT11, which can be identified in 30 to 50% of patients [2–7].

There is no specific treatment for MD. Several drugs of different classes are often used for symptomatic relief, but with poor efficacy or with intolerable side effects [1]. Deep brain stimulation (DBS) has been offered as a treatment for MD patients with refractory disabling symptoms and may allow drug dose reduction [8,9]. Forty-five MD patients treated with DBS have been reported in the literature to our knowledge. Because of the rarity of the disease, there are no randomized trials addressing the benefit of DBS. Although a review of the published cases shows a trend for a significant and consistent motor improvement with DBS, the benefit of the procedure is even less established in patients without *SGCE* gene mutations and there are insufficient data regarding effect on quality of life [10].

We add to this scarce literature two young patients with severe refractory MD treated with bilateral internal globus pallidus interna (GPi) DBS, one with genetically proven MD. We focus on changes in motor symptoms, disability and quality of life of these patients.

* Corresponding author. Tel.: +351 938 093 965; fax: +351 225 025 766.
E-mail address: helen.roch@gmail.com (H. Rocha).

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2. Methods

We describe two patients from different families with severe and refractory MD treated with bilateral GPi-DBS at the Centro Hospitalar São João, Portugal, in 2012 and 2013. The diagnosis of MD was established according to published criteria [3]. Genetic testing for *SGCE* mutations was performed in both patients. Demographic and clinical data were collected as well as details on surgical technique, stimulation parameters and adverse events.

Myoclonus was assessed using the total, rest and action subscores of the Unified Myoclonus Rating Scale (UMRS); dystonia was measured using the movement subscore of the Burke-Fahn-Marsden Dystonia Rating Scale (BFMRS). The functional subscore of the BFMRS was used to assess functional impairment. Both scales are scored in absolute values, and improvements are reported in percentages (modification of the absolute value before and after surgery). Parameters were collected before surgery and 6 and 12 months after surgery. To investigate the impact on quality of life the Portuguese translation of Medical Outcomes Study 36-item Short-Form General Health Survey, version 2.0 (SF-36v2) was used. This evaluation was performed before surgery and 12 months after DBS.

Patients or their legal representative gave written informed consent.

2.1. Patient 1

A 17-year-old boy had suffered brief, sudden and disabling jerks with abnormal posturing of the upper limbs since the age of six. His family history was negative for neurological or psychiatric disorders. He exhibited positive myoclonus at rest, more prominent during action, with predominance in the proximal upper limbs and trunk. He also had laryngeal and neck myoclonus causing dysarthria. Subtle cervical dystonia with right head tilt and mild dystonia of both hands were also present. Brain MRI was normal. There were no *SGCE* gene mutations identified and multiplex ligation-dependent probe amplification excluded point mutations as well as large gene deletions and rearrangements. Before surgery, the patient was on levetiracetam 1 g/day (valproic acid, zonisamide, clonazepam and propranolol had already been tried). Bilateral GPi-DBS was performed in November 2012 and benefits were sustained during 12 months of follow-up (Table 1). Mild dystonic posture of the right hand with hyperextension of the fingers and writer's cramp remained, without impact on daily living activities. The patient was able to successfully resume his school education and soon got his first job. Levetiracetam was withdrawn 6 months after surgery. No significant adverse effects were detected.

2.2. Patient 2

A 20-year-old man was noticed to have sudden, brief upper limb muscle jerking at the age of two. Those involuntary movements progressively worsened during adolescence and were exacerbated when performing simple daily tasks. Dystonic posture of his trunk, upper limbs and neck with laterocollis were progressively perceived. The patient's father and two paternal uncles also had alcohol-responsive myoclonus. Comprehensive investigations, including brain MRI, gave normal results. Psychiatric evaluation did not reveal any major disorder. When he was 18 years old, genetic testing for DYT11 revealed a *SGCE* gene point mutation in exon 2 (c.158C>D p.Ser53X), finally establishing the diagnosis of MD. The patient was taking clonazepam (3 mg/day), trihexifenidil (6 mg/day) and valproic acid (900 mg/day), without significant benefit.

At the age of 20, the patient underwent bilateral GPi-DBS surgery with marked benefit and without complications (Table 1), allowing drug dose reductions and valproic acid suspension.

2.3. Surgery and stimulation settings

Bilateral GPi-DBS was performed with stereotactic planning and microelectrode recordings, as previously described [11]. Monopolar settings were used, initially with a frequency of 130 Hz and pulse width of 60 microseconds. During the follow-up period those parameters were adjusted as appropriate, as shown in Table 2.

3. Results

Demographic and clinical data are listed in Table 1, as well as UMRS and BFMRS subscores for the individual patients. Only one patient had a mutation of the *SGCE* gene identified. The other patient had a diagnosis of probable MD according to the classification criteria of MD phenotype [3]. Follow-up time was 12 months.

Bilateral GPi-DBS improved motor symptoms of MD in both patients. Comparing results preoperatively and 12 months postoperatively, the mean improvement for myoclonus was 78.6% and 80.7% for Patient 1 and 2, respectively (Fig. 1A). Improvement in dystonia, as assessed by the BFMRS movement score, was 37% in Patient 1 and 86.7% in Patient 2 (Fig. 1B). At 12 months, the BFMRS disability subscore improved 71.4% for Patient 1 and 75% for Patient 2 (Fig. 1C).

Motor improvements remained stable between 6 and 12 months after surgery in Patient 1, except for a slight worsening in the BFMRS movement score. For Patient 2, there was marked improvements at 6 and 12 months after DBS, both in myoclonus and dystonia (Fig. 1).

Concerning quality of life, all parameters addressed by SF-36v2 improved or stabilized in both patients. The most prominent improvements were achieved in the role-physical, general health and social functioning domains (Table 3).

After 12 months of continuous stimulation, Patient 1 was off medication; Patient 2 suspended one of his drugs and was receiving significantly lower dosages of the remaining medications.

Table 1
Demographic and clinical data, including UMRS and BFMRS subscores for each patient with myoclonus-dystonia

Patient	Sex	Age at surgery	Symptom onset to surgery	*SGCE* gene mutation	UMRS					BFMRS				
						M0	M6	M12	M0 to M12 improvement		M0	M6	M12	M0 to M12 improvement
1	Male	17 years	11 years	Not identified	Rest	7	0	0	100%	Movement scale	9.5	4	6	37%
					Action	30	10	10	66.7%					
					Total	94	29	29	69.1%	Disability	7	2	2	71.4%
2	Male	20 years	18 years	c.158C>D p. Ser53X	Rest	25	6	5	80%	Movement scale	15	6	2	86.7%
					Action	62	10	5	91.9%					
					Total	111	38	33	70.3%	Disability	8	4	2	75%

BFMRS = Burke-Fahn-Marsden Dystonia Rating Scale, M0 = evaluation before surgery, M6 = evaluation 6 months after surgery, M12 = evaluation 12 months after surgery, SGCE = ε-sarcoglycan, UMRS = Unified Myoclonus Rating Scale.