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Clinical and Neurophysiological Improvement of SGCE Myoclonus-Dystonia with GPi Deep Brain Stimulation

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Abstract

Myoclonus-dystonia (M-D) is characterized by early onset myoclonus and dystonia. It is thought to be subcortical in origin. Response to oral medications may be incomplete, such that deep brain stimulation (DBS) surgery to the globus pallidum interna (GPi) or ventral intermediate thalamic nucleus (VIM) may be considered. The optimal site is not known. The physiology and surgical response for a 63 year-old woman who underwent GPi DBS for M-D with onset at age 2 and related

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to a mutation in the epsilon-sarcoglycan gene (*SGCE*) is described. She showed excellent clinical and neurophysiological improvement of both myoclonus and dystonia, suggesting that modulation by DBS is effective even after long disease duration and only partial response to oral medications.

Keywords

deep brain stimulation; myoclonus-dystonia; epsilon-sarcoglycan; surgery; neurophysiology; *SGCE*

1. INTRODUCTION

Myoclonus-dystonia (M-D) is characterized by early onset myoclonus and dystonia, and is usually alcohol responsive [1,2]. Many cases are due to mutations or deletions in the epsilon sarcoglycan gene (*SGCE*) [3,4]. Oral medications for either dystonia or myoclonus may not provide adequate symptom control or may lead to intolerable side effects, such that deep brain stimulation (DBS) surgery may be considered. However, the optimal anatomic target in M-D is unclear, as there are reports in the literature of benefit from DBS targeting both the globus pallidus pars interna (GPi) [5–10] and ventral intermediate thalamic nucleus (VIM) [11,12] and clinical trials comparing the two targets are lacking. We report detailed physiology and clinical follow-up for a 63 year-old woman who underwent DBS for genetically confirmed M-D. She showed excellent and long-standing clinical and neurophysiological improvement of both myoclonus and dystonia.

2. CASE REPORT

This sixty-three year old right-handed woman had onset of muscle jerking at age two. The jerks began in her legs, and worsened and spread around menarche to her trunk, neck and arms. She also noted neck pulling and leg twisting. Action and stress exacerbated the movements, while drinking alcohol attenuated them, which led to frequent alcohol use. She was able to carry out household chores independently, but would avoid eating in public and never drove a car. Brief clinical features, and her frameshift mutation in exon 7 of epsilon-sarcoglycan (*SCGE*) have been previously reported [4,13].

On initial neurological exam at age fifty-five there was diffuse multifocal myoclonus and dystonia with intermittent lip pursing, eye closing, jerky tremors in the neck, voice, trunk and all four limbs, and mild dystonic posturing of the right foot and leg during certain motor tasks and with walking. While writing, she exhibited dominant arm abduction and extension with myoclonic jerks, prominent retro and laterocollis and trunk extension. Pouring elicited truncal and cervical dystonia and myoclonus. She also displayed retropulsion on the pull test (Unified Parkinson's Disease Rating Scale, UPDRS [14], rating of 2). EEG, MRI and serum ceruloplasmin levels were normal. Symptoms suggestive of obsessive-compulsive disorder (OCD) were reported by a family member but the patient did not endorse these at neuropsychological evaluation. Primidone (250 mg/day), propranolol (180 mg/day), chlordiazepoxide (100 mg/day), and levetiracetam (2500 mg/day) were discontinued due to lack of benefit. Additional trials of gabapentin and carbidopa/levodopa were also ineffective. Trihexyphenidyl (5 mg/day) was partially effective in treating leg and cervical dystonia, but caused visual hallucinations and paranoia. Sodium oxybate (2 g/day) was partially efficacious but discontinued due to emesis. Clonazepam (3.5 mg/day) and valproate (1750 mg/day) provided mild to moderate improvement of myoclonus. Because of insufficient medication response, at age 63, she underwent bilateral globus pallidus interna (GPi) DBS surgery. GPi was targeted because both dystonia and myoclonus were disabling features and GPi is considered the target of choice for primary dystonia [15–20].

2.1 Deep brain stimulation implant

Surgery was performed following established DBS procedures. The anatomic target was based on a stereotactic atlas with coordinates relative to the mid-commisural point of 2mm anterior, 20mm lateral and 5mm inferior. Microelectrode single unit recording was used to map the GPI prior to implantation of quadripolar stimulation electrodes (Medtronic, Inc., Minneapolis, MN). Post-operative imaging analyzed on the stereotactic planning software and the active electrode confirmed placement within 2mm of the planned target. Soletra (Medtronic Inc., Minneapolis, MN) pulse generators were subsequently implanted.

2.2 Clinical evaluation

Fourteen months after surgery, with optimal stimulation settings using bilateral monopolar fields (C+1-) at 2.0 V, 180 μ s and 135 Hz, she reported remarkable quality of life improvement, including being able to carry her infant grandchild and eat in public. Of note, pre-operatively and post-operatively, the patient was no longer using alcohol, but was taking clonazepam and valproate. The dose of both medications post-operatively was approximately 50% of the pre-operative dose.

Blinded videotape reviews with Fahn-Marsden Dystonia-Rating Scale [21] (FM) were performed for all examinations except one month preoperatively. Eight years prior to surgery at age 55, her FM motor section (/120) was 40.5, one month preoperatively was 38 and fourteen months after surgery her score was 22.5. She had occasional leg and neck myoclonus with action, still worse when writing. Moderate posterior neck pain persisted, although larger amplitude neck jerks became less frequent. Despite dramatic improvement in myoclonus and dystonia, her retropulsion did not improve (post-operative UPDRS rating 2).

2.3 Neurophysiology

Neurophysiological testing was performed three times: initially (eight years prior to surgery), one week pre-operatively and fourteen months post-DBS implantation using multi-channel surface electromyography (EMG) Ag/AgCl bipolar electrodes. The active leads were placed over the patient's most clinically involved muscle bellies (bilateral sternocleidomastoid, trapezius, and tibialis anterior muscles). Recordings were digitized with a 14 bit A/D system, sampled at 500 Hz in 4 to 10 second intervals, and band-pass filtered at 30 Hz - 10 KHz. Data were acquired and analyzed using semiautomatic interactive software developed in the Clinical Motor physiology Laboratory. EMGs from all channels were full-wave rectified and integrated to compare EMG timing and burst durations. EMG frequencies were calculated using discrete Fast Fourier transform methods to generate autocorrelation spectra from the rectified/integrated EMG signals. Initial testing detected 50–200 ms burst discharges with flat baseline between bursts, consistent with myoclonus, and longer duration 600–1000 ms periods of muscle activity consistent with dystonia (Fig 1 A). At rest, these spasms were only present in the tibialis anterior bilaterally. With action, such as extending the arms and writing, activity spread to her neck muscles and burst power and frequency increased, resulting in 3.5–5.5 Hz semi-rhythmic tremor-like EMG patterns with flat baseline activity between burst discharges.

On pre-operative assessment, eight years after initial evaluation and a week prior to surgery, her EMG profile showed continuous 3.8–4.7 semi rhythmic 50–150 ms myoclonic bursts of activity in both legs. With any action, there were longer duration 600–1000 ms dystonic bursts, with superimposed higher amplitude myoclonus in the leg and neck muscles (Fig 1 B).

Post-operative testing quantified substantial decrease in abnormal EMG bursts: there were no longer spasms at rest and only occasional 50–200 ms myoclonus with action, without associated dystonic activity (Fig 1 C).

3. DISCUSSION

We report the long-term clinical and electrophysiological result of bilateral globus pallidus stimulation in a 63-year old woman with disabling myoclonus-dystonia due to a mutation in the epsilon-sarcoglycan gene. Our case is remarkable for several reasons, including the long disease duration prior to surgery, the extensive electrophysiological follow-up, and the lack of improvement of postural stability despite marked improvement of myoclonus and dystonia.

The optimal stimulation target for deep brain stimulation in medication-refractory M-D is unclear. Functional neuroimaging reports are scarce, pointing to the thalamus and striatum as possible DBS targets [22,23]. The myoclonus is believed to be subcortical in origin [24–26], and disability in M-D may be related to both myoclonus and dystonia. Electromyography demonstrates both myoclonic and dystonic features: there are bursts of 30–1500 ms duration, and a spectrum of intermediate burst length that can be synchronous and symmetrical, or asymmetrical and asynchronous, and present in single muscles or co-contracting antagonist muscles [1], and myoclonic bursts of 25–250 ms duration present at rest and exacerbated by action and posture [24].

There have been several prior reports of DBS in patients with M-D. Six patients with confirmed *SCGE* mutations (ages 8–39) and five adults without genetic testing (ages 26–51) have undergone bilateral GPi surgery with significant improvement [5–10]. Ventral intermediate thalamic stimulation in a two adults (ages 60 and 74) with inherited M-D syndrome, one genetically confirmed, effectively reduced myoclonus but not dystonia [11,12]. To our knowledge, this is the oldest person with M-D to have undergone pallidal DBS. This is in contrast to a report of GPi deep brain stimulation in primary dystonia which demonstrates a better response at younger age and it is inferred that older participants may not respond well [27]. The improvement in FM scores in our case was similar to the one reported by Cif et al. [7] for a boy with seven years of disease duration, suggesting that disease duration does not appear to play a significant role in the response to DBS in M-D.

Parkinsonian features, including rest tremor, abnormal pull test, low dopaminergic metabolites and response to levodopa have been reported in a minority of M-D patients [4,28]. However, an etiological connection to *SGCE* has not been established. Whether these clinical features are a manifestation of myoclonus and dystonia, rather than true parkinsonism is unclear. While this patient did not improve with levodopa, the persistent postural instability after significant improvement of myoclonus and dystonia suggests that parkinsonism may be an independent, albeit uncommon, feature of M-D. Abnormal dopaminergic and 5-HT metabolites have been demonstrated in a mouse model of M-D, although a hyperdopaminergic rather than hypodopaminergic state was postulated [29]. Alterations in sensory integration which have been demonstrated in subjects with dystonia [30] and impaired vestibular reflexes [30,31] may be alternative explanations for the postural instability. However, postural control of cervical dystonia patients was found to be very similar to that of control subjects [33].

As demonstrated neurophysiologically, there was substantial decrease in the frequency and amplitude of myoclonus and suppression of dystonia with GPi stimulation. This suggests that in M-D, the pallidum plays a role in generation, or at least modulation, of both these hyperkinetic features. The expression of shorter (myoclonic) or longer duration (dystonic) EMG bursts could depend on differences in pallidal neurons discharge patterns, degree of synchronization and varying responsiveness to sensory input [10,34].

Without randomization between pallidal and thalamic stimulation it cannot be definitively determined which site is optimal for DBS in M-D. Until such time, this report supports that M-D patients may significantly benefit from GPi DBS. In our case, excellent response was noted more than sixty-one years after onset of symptoms, suggesting that significant

modulation by DBS is possible, even after long disease duration and relative treatment refractoriness. Larger studies of M-D patients are needed to confirm whether GPi is the optimal target and whether mutation type may influence surgery outcome.

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Figure 1.

Three columns (first, pre- and post-operative evaluations) of raw surface EMG recordings (on the left) are paired with fast Fourier transforms (FFT) after rectification and integration (on the right). Representative traces are shown for three conditions (at rest, with arms extended and writing). Three channels: right (R), left (L) tibialis anterior (TA) and left sternocleidomastoid (SCM) are displayed.

Typical dystonic bursts are underscored, and the first three of the myoclonic discharges in each segment are marked with arrows. EMG gains and FFT power are normalized across all recordings. Four seconds of EMG at = 500 μV /division are displayed.

Note the superimposition of myoclonic and dystonic EMG activity. Note also the multi-peaked (predominantly 4–7 Hz) activity EMG burst discharges pre-operatively in all channels, and the decreased activity after GPi DBS. Dystonic activity has disappeared while very low power myoclonic EMG discharges remain post-operatively.

Table 1

Reports of *SCGE* mutation positive Myoclonus-Dystonia with DBS

Author	Age/Gender	Predominant Clinical Manifestation (s)	DBS Settings		Improvement measures
GPI					
Cif et al.[7]	8/M	Myoclonus, Dystonia	Frequency (Hz)	Stimulus duration (μsec)	Voltage (V)
			130	450	0.8–1.3
					86%*, 94%**, 70%***
Foncke et al.[10]	39/F	Myoclonus, Dystonia	Not reported	Not reported	Not reported
					59%*, 95%**, 79%***
	18/M	Myoclonus, Dystonia	Not reported	Not reported	Not reported
					60%*, 78%**, 90%***
Kurtis et al.	63/F	Myoclonus, Dystonia	135	180	2.0
					70%*
VIM					
Kuncel et al.[12]	74/F	Myoclonus	185	60–90	1.5–2.8
					53%**, 14%***

* FM, Fahn-Marsden Dystonia Rating Scale [21]

** UMRS, Unified Myoclonus Rating Scale [35] action myoclonus score.

*** UMRS, Unified Myoclonus Rating Scale functional score.