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Tremor and Other Hyperkinetic Movements

Brief Reports

Improvement of Post-hypoxic Myoclonus with Bilateral Pallidal Deep Brain Stimulation: A Case Report and Review of the Literature

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Abstract

Background: Post-hypoxic myoclonus (PHM) is a syndrome that occurs when a patient has suffered hypoxic brain injury. The myoclonus is usually multifocal and generalized, often stemming from both cortical and subcortical origins. In severe cases, pharmacological treatments with antiepileptic medications may not satisfactorily control the myoclonus.

Methods: We present a case of a 23-year-old male with chronic medication refractory PHM following a cardiopulmonary arrest related to an asthmatic attack who improved with bilateral globus pallidus internus (GPi) deep brain stimulation (DBS). We review the clinical features of PHM, as well as the preoperative and postoperative Unified Myoclonus Rating Scale scores and DBS programming parameters in this patient and compare them with the three other published PHM-DBS cases in the literature.

Results: This patient experienced an alleviation of myoclonic jerks at rest and a 39% reduction in action myoclonus with improvement in both positive and negative myoclonus with bilateral GPi-DBS. High frequency stimulation (130 Hz) with amplitudes >2.5 V were needed for the therapeutic response.

Discussion: We demonstrate a robust improvement in a medication refractory PHM patient with bilateral GPi-DBS, and suggest that it is a viable therapeutic option for debilitating post-hypoxic myoclonus.

Keywords: Post-hypoxic myoclonus, deep brain stimulation, globus pallidus internus

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Introduction

The syndrome of post-hypoxic myoclonus (PHM) emerges within days to weeks of a patient suffering hypoxic brain injury, usually from cardiopulmonary arrest (CPA).[1,2] PHM is commonly cortical, manifesting as multifocal, generalized muscle jerks that increase during movement and/or accentuate with sensory stimuli.[3] Subcortical, brainstem myoclonus can often coexist. First described by Lance and Adams,[1] PHM can also be associated with other neurological symptoms including cerebellar ataxia and seizures. Myoclonus may be positive or negative, and patients usually have a combination of cortical/subcortical and positive/negative myoclonus.

Treatment for chronic myoclonus is difficult, requiring a polypharmacy approach using antiepileptic medications such as levetiracetam, piracetam, clonazepam, and valproate.[4,5] Primidone, valproate, and clonazepam are usually insufficient monotherapies and their side effects can exacerbate the underlying myoclonus.[6] Levetiracetam and piracetam have been shown in clinical trials to be tolerable and effective in cortical myoclonus,[7,8] but the high doses needed for these drugs can engender non-compliance. As a result, patients with PHM usually require a combination of the classes of aforementioned medications with variable responses. Deep brain stimulation (DBS) has

Video 1. Myoclonus at rest and with action. Cortical and subcortical myoclonus affecting the patient's speech and limb movements.

Video 2. Myoclonic volley. Episode of myoclonic volley with frequent generalized myoclonus at rest and with action.

been suggested in patients with chronic PHM, but there have been only three reported cases of PHM treated with DBS.[9–11] We report a fourth case of a patient with PHM following an asthmatic attack and CPA who was effectively treated with DBS, and only the second case to utilize bilateral globus pallidus internus (GPi) stimulation. We suggest that this approach should be considered in patients with severe disability from PHM when medications fail.

Case

A 23-year-old male with a history of asthma and gastric bypass surgery suffered an asthmatic attack en route to a scheduled endoscopy. He went into cardiopulmonary arrest and was resuscitated after three rounds of defibrillation and cardiopulmonary resuscitation for 15 minutes. Within 24 hours of this event, he developed generalized and multifocal myoclonus while in intensive care and was comatose for approximately 1 month before regaining consciousness. Electroencephalogram monitoring did not reveal seizure activity. He underwent a tracheostomy and a percutaneous endoscopic gastrostomy, both of which were eventually reversed. He was referred to our center 2 years after the hypoxic and despite early gains in his mental status, respiratory function and dysphagia, his myoclonus persisted—occurring at rest and worsened with movement of his hands and legs. He was unable to hold a cup with either hand because of action myoclonus (Video 1). He required assistance with all activities of daily living and was unable to ambulate more than a few steps even using a walker. Throughout the day he had several episodes of myoclonic "volleys," characterized as frequent, relentless flurries of generalized myoclonus that would last 20 minutes to 1 hour (Video 2). The patient would sweat profusely during these events and consumption of several shots of vodka was found to substantially dampen the myoclonus. A regimen of levetiracetam 1,500 mg twice a day, clonazepam 2 mg three times a day, and valproate 250 mg three times a day provided only modest control of his rest and action myoclonus and further increases failed to decrease the severity or frequency of his myoclonic volleys.

On examination, while in the seated position, there were mild spontaneous myoclonic jerks in his arms and hands. His speech was incomprehensible with frequent arrests. He had one or two jerks of his neck when rotating his head and infrequent facial myoclonus. Action

Video 3. Myoclonus when standing. Negative myoclonus observed in the patient's legs when standing.

myoclonus emerged when his arms were outstretched and increased on finger to nose movements with myoclonic jerks in flexor more than extensor muscle groups. There was no stimulus-induced myoclonus with tactile or pinprick stimulation of the arms or legs. He required two-person assistance to stand, which triggered negative myoclonus in his legs with frequent truncal jerks (Video 3). His stance was broad based and he was unable to take a step forward.

Following a multidisciplinary deliberation that took into consideration this patient's preserved cognition, lack of other medical comorbidity, and severity of disability stemming from medication refractory myoclonus, a recommendation for DBS was taken as an attempt to recuperate some level of meaningful quality of life. The decision to choose bilateral GPi as the target for implantation was in part based on our experience along with published data of treating myoclonus in myoclonus–dystonia patients with GPi-DBS.[12–15]

Methods

The patient underwent staged implantation of bilateral DBS electrodes (Medtronic 3389, Medtronic Inc., St. Paul, MN) 3 years after his anoxic event. The electrodes were placed into the posteroventrolateral globus pallidus internus using a Leksell stereotactic frame and O-Arm guidance. The operative target was localized as 20 mm lateral to the

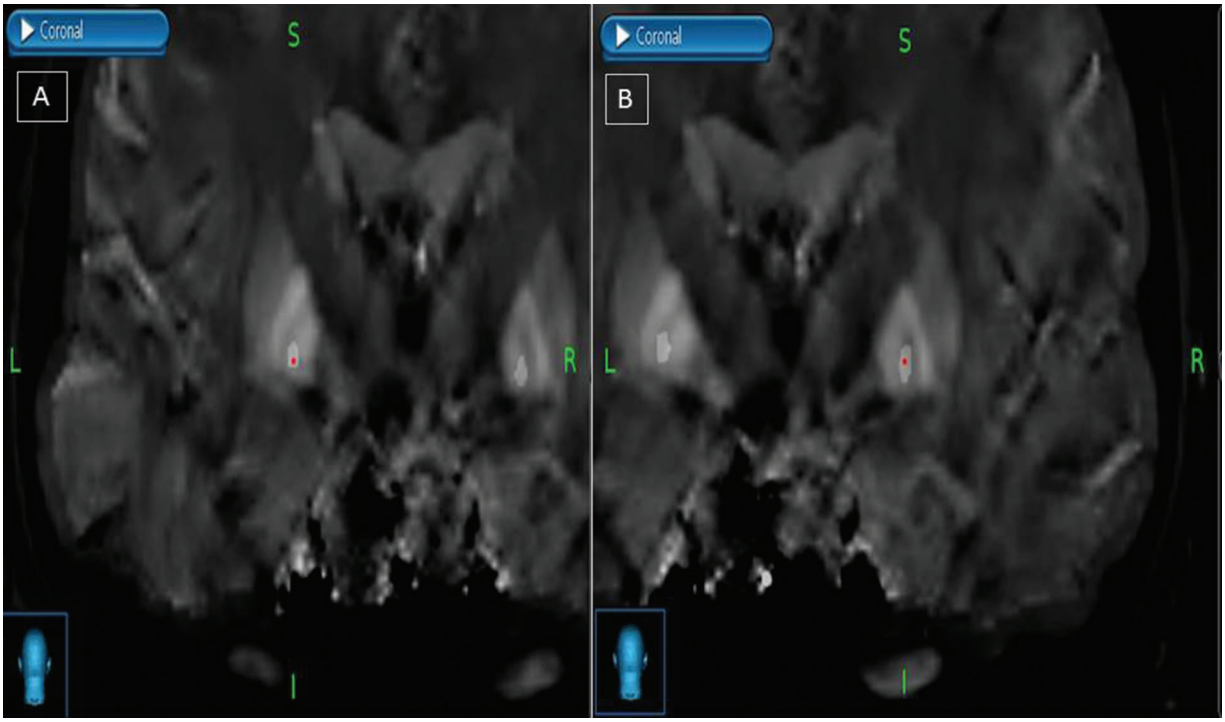

Figure 1. **Bilateral DBS electrode position**. Preoperative magnetic resonance imaging quantitative susceptibility mapping of coronal sequences showing the co-registered postoperative computed tomography location of the centroid (red dot) of the left (A) and right (B) electrodes in the globus pallidus internus.

midline, 2.5 mm anterior to the middle cerebral peduncle (MCP), and 4 mm inferior to the commissural line. The target was then cross correlated with the reformatted Schaltenbrand and Wahren atlas and with the Quantitative Susceptibility Mapping (QSM)[16] images showing the GPi. Intraoperative microelectrode recording provided further targeting refinement and a postoperative CT co-registered with preoperative magnetic resonance imaging provided confirmation of electrode placement (Figure 1).

Results

Postoperative programming commenced 2 weeks after the pulse generators were implanted. Of note, there was no objective clinical change in the patient's physical condition or functional improvement before stimulation started. Initial programming consisted of a monopolar review (pulse width (PW) 90 ms, frequency 130 Hz) that evaluated each contact and mapped their myoclonus reduction along with any unwanted side effects. There was immediate reduction of both rest and action myoclonus, greater on the left hemibody during initial programming. However, he developed an infection of the left implanted pulse generator (IPG) 2 months from initial programming that spared the left electrode. The IPG was removed, and as a result his right upper extremity rest and action myoclonus returned. Following 6 weeks of antibiotics, his IPG was reimplanted.

Six months from the first programming session, there was only mild action myoclonus in both his arms and legs. His lower extremity negative myoclonus also showed improvement by this time following a very modest rate of response up until that point. This allowed him to stand by pushing off with both hands and walk several meters using a walker in physical therapy with one-person assistance. He was able to hold items with each hand, drink from a cup with one hand, and open a bottle cap (Video 4). He started brushing his teeth independently and assisted his caretakers with dressing and hygiene. In addition, his myoclonic volleys were no longer a daily occurrence.

Video 4. 6 months after with Bilateral GPi-DBS. Reduction in myoclonus with pallidal deep brain stimulation. The patient is able to drink from a water bottle, push himself up to stand, and takes a few steps with assistance.

Programming parameters and changes in his Unified Myoclonus Rating Scale Motor scores from an unblinded rater are shown in Table 1 along with the three other published PHM-DBS cases. His action myoclonus in his arms required large stimulation amplitudes. Furthermore,

Table 1. **Post-hypoxic Myoclonus Cases Treated with Deep Brain Stimulation**

	Age/ Gender	Etiology	Body Region Affected	Preoperative UMRS			Postoperative UMRS			Medication	DBS Target/ Electrode	DBS Parameters (contacts: amplitude/PW/ Freq)
				Rest	Action	Stimulus Sensitive	Rest	Action	Stimulus Sensitive			
Yamada et al.[9]	71M	Right putaminal hemorrhage and CPA	Right Hemibody	24	52	NA	6	15	NA	Clonazepam (1.5 mg/day) Valproate (800 mg/day) Gabapentin (400 mg/day)	Left Gpi (Medtronic 3387)	L: 1–2+1, 8V/450 μs/130 Hz
Kobayashi et al.[10]	36M	Perinatal anoxia	Upper limbs	NA	LUE 12 RUE 9	NA	NA	LUE 2 RUE 2	NA	N/A	B/L VIM (Medtronic 3387)	R: 1–3+ settings unavailable L: 1–3+ settings unavailable
Asahi et al.[11]	54M	CPA	Generalized	8	25	5	0	5	0	Valproate acid Clonazepam Intrathecal Baclofen	BL Gpi (Medtronic 3387)	Interleaved R: 1(–) 2(+) 2.5 V/ 60 μsec/125 Hz L: 0(–) 1(+) 2.0 V/ 60 μs/125 Hz
Current case	26M	Asthmatic attack and CPA	Generalized	75[1]	52 RUE 6 RLE 2 LUE 6 LLE 2	0	0	32 RUE 2 RLE 2 LUE 0 LLE 2	0	Clonazepam (6 mg/day) Levetiracetam (3,000 mg/ day) Valproate (750 mg/day)	BL Gpi Medtronic/ 3389	R: 3-c+: 2.8 V/ 90 μs/130 Hz L: 1-2-3-C+: 2.5 V/ 60 μs/130 Hz

Abbreviations: CPA, Cardiopulmonary Arrest; LLE, Left Lower Extremity; LUE, Left Upper Extremity; NA, Not Available; RLE, Right Lower Extremity; RUE, Right Upper Extremity; UMRS, Unified Myoclonus Rating Scale.

[1]Assessed during an episode of a myoclonic volley.

Table 2. **Neuroimaging Findings in Post-Hypoxic Myoclonus**

Study	No. Patients	Imaging Modality	Results
Frucht et al.[20]	7	FDG-PET	Bilateral increase in glucose metabolism in pontine tegmentum, ventrolateral thalamus, and medial temporal lobes
Carbon et al.[21]	7	FDG-PET	Conjunction analysis with DYT-11 revealed shared increases in parasagittal cerebellar nuclei bilaterally
Park et al.[22,a]	1	rs-fMRI	Increased connectivity between: 1) primary motor cortex and right somatosensory association cortex 2) primary sensory cortex and left visual association cortex 3) supplementary motor cortex and right inferior temporal, right orbito-temporal, left primary auditory, and left somatosensory association cortex
Ferlazzo et al.[23]	1	Serial MRIs	4 days after CPA, DWI lesions in cerebellum and thalami, FLAIR was normal 20 days after CPA–DWI and FLAIR normal 6 months after CPA–3T MRI with quantitative volumetric analysis no atrophy of thalami, cerebellum, caudate nuclei, putamina, pallidus nuclei, hippocampi, as well as normal volumes of whole encephalic tissue, gray and white matter
Werhahn et al.[2,b]	14	MRI	Mean 2.5 years from CPA: 4 patients – mild cortical and cerebellar atrophy 4 patients – hemispheric or cerebellar infarcts 4 patients – normal
Zhang et al.[24]	2	SPECT MRS FDG-PET	1 patient 2 months from CPA SPECT – revealed mild left temporal lobe hypoperfusion 1 patient 10 months from CPA MRS – moderate reduction in N-acetyl aspartate peak in her left hippocampus and a mild decrease in the right hippocampus PET – metabolic reduction in frontal lobes
Huang et al.[25]	1	fMRI	Increased BOLD bilateral cortical areas, particularly the motor cortex of legs. Of note patient has only muscle jerks in her legs

Abbreviations: BOLD, Blood Oxygenation Level Dependent; CPA, Cardiopulmonary Arrest; DWI, Diffusion-weighted Image; FDG-PET, [^{18}F]-fludeoxyglucose-positron Emission Tomography; MRS, Magnetic Resonance Spectroscopy; PET, Positron Emission Tomography; rs-fMRI, Resting State Functional Magnetic Resonance Imaging; SPECT - Single-photon emission computed tomography.
[a]One post-hypoxic myoclonus patient compared with four age matched controls
[b]12 of 14 PHM patients had brain MRI.

a tripolar configuration of the left DBS was used to create a broad stimulation field as a means to attenuate his right upper extremity myoclonus.

As a result of reduced PHM, the patient's underlying mild appendicular dysmetria and gait ataxia, which were not initially appreciated because of the extent of his muscle jerks, were unmasked, and remained unresponsive to stimulation. His myoclonic medications also remained unchanged as attempts to reduce them increased his myoclonus.

Discussion

Though neurophysiological studies were not conducted, phenomenologically this patient manifested both chronic cortical and subcortical myoclonus. The presence of multifocal, distal muscle jerks that increased with movement was consistent with a cortical process. Subcortical or reticular myoclonus was evident with observed jerks in his face, neck, and proximal upper extremity flexor muscles during movement, as well as negative myoclonus in his legs.[17,18]

Pallidal and thalamic DBS have been shown to be quite effective in suppressing myoclonus, especially in patients with myoclonus–dystonia.[12,13] However, to the best of our knowledge, there have only been three reported cases of PHM treated with DBS (Table 1). Two of those cases were pallidal stimulation—one of which was unilateral to treat hemimyoclonus following a stroke,[9] while the other was a bilateral implantation that effectively treated CPA-induced myoclonus in all extremities.[11] Khobayashi et al.[10] reported a case of perinatal

anoxia-induced action myoclonus successfully treated with bilateral VIM-DBS. The programming parameters for these cases all utilized a bipolar configuration to achieve therapeutic gain, whereas a monopolar and tripolar configuration in our patient, produced robust responses at amplitudes >2.5 V without any side effects.

The pathophysiology of post-hypoxic myoclonus remains unknown. However, the rat arrest model with myoclonus[19] demonstrated degeneration in pyramidal cells of layers III and IV of the cerebral cortex and reticular thalamus along with extensive Purkinje cell damage in the cerebellum. Concomitantly, decreases in 5-HTP (hydroxytryptophan), 5-HT (hydroxytryptamine receptors), and 5-HIAA (hydroxyindoleacetic acid) in the cortex, mesencephalic regions, striatum, and cerebellum highlighted a potential role of the serotonergic system in the pathophysiology of PHM. Recent human brain imaging studies in PHM showed minimal anatomical changes but significant cortical and cerebellar connectivity, metabolic, and blood flow changes[2,20–25] (Table 2). Of note, fludeoxyglucose positron emission tomography findings by Frucht and colleagues[20] revealed elevated glucose metabolism in the ventrolateral thalamus and pontine tegmentum in seven patients with PHM, suggesting involvement of the basal ganglia-thalamocortical network. When compared to myoclonus–dystonia (DYT-11), shared metabolic increases were seen in the parasagittal cerebellar nuclei.[21] Combining these findings with the neuronal injury in the paravermal and vermal regions of the rat arrest model, suggests that dysfunctional ascending pathways intricate to motor execution[19] are contributory to the generation of PHM. Furthermore, the unmasking of cerebellar symptoms following attenuation of our patient's myoclonus underscores the potential putative role of the cerebellum in the pathogenesis of myoclonus, especially cortical myoclonus.

There are limited data regarding the neuronal activity of the GPi in the context of PHM. However, aberrations in GPi neuronal recordings have been reported in a constellation of hyperkinetic disorders such as myoclonus–dystonia,[26] generalized and secondary dystonia, and hemiballismus.[27,28] The response of cortical myoclonus to pallidal stimulation in this patient suggests the possibility that dysfunctional motor cortical relays and/or cerebellar efferents converge on the basal ganglia–thalamocortical network triggering changes in the nature of neuronal processing. Unlike cortical myoclonus, the pathophysiology of subcortical myoclonus is less clear; however, its response to stimulation infers a possible role for this network in its pathogenesis.

In summary, we present a patient with medication-refractory post-hypoxic myoclonus following cardiopulmonary arrest manifesting with cortical (positive and negative myoclonus) and subcortical myoclonus who experienced significant improvement with pallidal deep brain stimulation. Based on our growing understanding of the pathophysiology of cortical myoclonus as well as the robust nature by which it responds to DBS in myoclonus–dystonia and a small cohort of published PHM cases, it is not unreasonable to consider DBS as a therapeutic option in debilitating Lance Adam's syndrome.

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