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

Citation: Ramdhani RA, Frucht SJ, Kopell BH. Improvement of post-hypoxic myoclonus with bilateral pallidal deep brain stimulation: a case report and review of the literature. Tremor Other Hyperkinet Mov. 2017; 7. doi: 10.7916/D8NZ8DXP

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 accentuated 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.5,6 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...
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 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 posterolateral globus pallidus internus using a Leksell stereotactic frame and O-Arm guidance. The operative target was localized as 20 mm lateral to the
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) 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.

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/430 μs/130 Hz |
| Kobayashi et al.10 | 36M | Perinatal anoxia | Upper limbs | NA | LUE 12 | RUE 9 | 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 | Valproic acid | Clonazepam | Intrathecal Baclofen | BL Gpi (Medtronic 3387) | Interleaved | R: | 1-3+ settings unavailable | L: 1-3+ settings unavailable |
| Current case | 26M | Asthmatic attack and CPA | Generalized | 75 | 52 | RUE 6 | RLE 2 | LUE 6 | LLE 2 | 0 | 0 | 32 | RUE 2 | RLE 2 | LUE 0 | LLE 2 | Clonazepam (6 mg/day) | Levetiracetam (3,000 mg/day) | Valproic acid (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/125 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.
1Assessed during an episode of a myoclonic volley.
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

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 thalamus, FLAIR was normal 20 days after CPA–DWI and FLAIR normal 6 months after CPA–3T MRI with quantitative volumetric analysis no atrophy of thalamus, 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.
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 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 (hydroxyindolacetic 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 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 (positive and negative myoclonus) and subcortical (dyt 11), shared metabolic increases were seen in the parasagittal thalamocortical network. When compared to myoclonus–dystonia patients with PHM, suggesting involvement of the basal ganglia–thalamocortical network.

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.

References

1. Lance JW, Adams RD. The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain* 1963;86:111–136. doi: 10.1093/brain/86.1.111
2. Werhahn KJ, Brown P, Thompson PD, Marsden CD. The clinical features and prognosis of chronic posthypoxic myoclonus. *Mov Disord* 1997;12:216–20. doi: 10.1002/mds.870120212
3. Hallett M. Physiology of human posthypoxic myoclonus. *Mov Disord* 2000;15 (Suppl. 1):8–13. doi: 10.1002/mds.870150703
4. Fahr S. Post-anoxic action myoclonus: improvement with valproic acid. *Neurol J Engl* 1978;299:313–314.
5. Obeso JA. Therapy of myoclonus. *Clin Neurol* 1995;3:253–257.
6. Ikeda A, Shihasaki H, Tashiro K, Mizuno Y, Kimura J. Clinical trial of piracetam in patients with myoclonus: nationwide multistitution study in Japan. The Myoclonus/Piracetam Study Group. *Mov Disord* 1996;11:691–700. doi: 10.1002/mds.870110615
7. Striano P, Manganelli F, Boccella P, Perretti A, Striano S. Leviteracem in patients with cortical myoclonus: a clinical and electrophysiological study. *Mov Disord* 2005;20:1610–1614. doi: 10.1002/mds.20530
8. Frucht SJ, Louis ED, Chuang C, Fahn S. A pilot tolerability and efficacy study of leviteracem in patients with chronic myoclonus. *Neurology* 2001;57:1112–1114. doi: 10.1212/WNL.57.6.1112
9. Yamada K, Sakurama T, Soyama N, Kuratsu J. Gpi pallidal stimulation for Lance-Adams syndrome. *Neurology* 2011;76:1270–1272. doi: 10.1212/WNL.0b013e3182148284
10. Kobayashi K, Katayama Y, Otaka T, et al. Thalamic deep brain stimulation for the treatment of action myoclonus caused by perinatal anoxia. *Stem Cell Res Ther* 2010;18:259–263. doi: 10.1159/000315464
11. Asahi T, Kashiwazaki D, Douga N, et al. Alleviation of myoclonus after bilateral pallidal deep brain stimulation for Lance-Adams syndrome. *J Neurol* 2013;260:1501–1503. doi: 10.1007/s00415-015-7740-x
12. Ramdhani RA, Frucht SJ, Behnegar A, Kopell BH. Improvement of isolated myoclonus phenotype in myoclonus dystonia after pallidal deep brain stimulation. *Tremor Other Hyperkletant Mov* 2016;6. doi: 10.7916/DIF47P0C
13. Gruber D, Kuhn AA, Schoenecker T, et al. Pallidal and thalamic deep brain stimulation in myoclonus-dystonia. *Mov Disord* 2010;25:1733–17343. doi: 10.1002/mds.23312
14. Azoulay-Zys J, Roze E, Welter ML, et al. Bilateral deep brain stimulation of the pallidum for myoclonus-dystonia due to epsilop-sarcoglycan mutations: a pilot study. *Arch Neurol* 2011;68:94–98. doi: 10.1001/archneurol.2010.338
15. Kurtis MM, San Luciano M, Yu Q, et al. Clinical and neurophysiological improvement of SGCE myoclonus-dystonia with Gpi deep brain stimulation. *Clin Neurol Neurosurg* 2010;112:149–152. doi: 10.1016/j.clineuro.2009.10.001
16. Deistung A, Schafer A, Schwere F, Bierdermann U, Turner R, Reichenbach JR. Toward in vivo histology: a comparison of quantitative susceptibility mapping (QSM) with magnitude-, phase-, and R2*-imaging at ultra-high magnetic field strength. *Neuroimage* 2013;65:299–314. doi: 10.1016/j.neuroimage.2012.09.055
17. Tassinari CA, Rubboli G, Shihasaki H. Neurophysiology of positive and negative myoclonus. *Electroencephalogr Clin Neurophysiol* 1998;107:181–195. doi: 10.1016/S0003-4694(98)00058-3
18. Rubboli G, Tassinari CA. Negative myoclonus. An overview of its clinical features, pathophysiological mechanisms, and management. *Neurophysiol Clin* 2006;36:337–343. doi: 10.1016/j.neucli.2006.12.001

19. Tai KK, Bhidayasiri R, Truong DD. Post-hypoxic animal model of myoclonus. *Parkinsonism Relat Disord* 2007;13:377–381. doi: 10.1016/j.parkreldis.2007.07.001

20. Frucht SJ, Trost M, Ma Y, Eidelberg D. The metabolic topography of posthypoxic myoclonus. *Neurology* 2004;62:1879–1881. doi: 10.1212/01.WNL.0000125336.05001.23

21. Carbon M, Raymond D, Ozelius L, et al. Metabolic changes in DYT11 myoclonus-dystonia. *Neurology* 2013;80:385–391. doi: 10.1212/WNL.0b013e318270798

22. Park KM, Han YH, Kim TH, et al. Increased functional connectivity between motor and sensory cortex in a patient with Lance-Adams syndrome. *Clin Neurol Neurosurg* 2015;139:241–243. doi: 10.1016/j.clineuro.2015.10.021

23. Ferlazzo E, Gasparini S, Cianci V, Cherubini A, Aguglia U. Serial MRI findings in brain anoxia leading to Lance-Adams syndrome: a case report. *Neurou Sci* 2013;34:2047–2050. doi: 10.1007/s10072-013-1356-2

24. Zhang YX, Liu JR, Jiang B, et al. Lance-Adams syndrome: a report of two cases. *J Zhejiang Univ Sci B* 2007;8:715–720. doi: 10.1631/jzus.2007.B0715

25. Huang HC, Chen JC, Lu MK, Chen JM, Tsai CH. Post-hypoxic cortical myoclonus mimicking spinal myoclonus - electrophysiological and functional MRI manifestations. *Eur J Neurol* 2011;18:e4–5. doi: 10.1111/j.1468-1331.2010.03186.x

26. Welter ML, Grabli D, Karachi C, et al. Pallidal activity in myoclonus dystonia correlates with motor signs. *Mov Disord* 2015;30:992–926. doi: 10.1002/mds.26244

27. Vitek JL, Chockkan V, Zhang JY, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. *Ann Neurol* 1999;46:22–35. doi: 10.1002/1531-8249(199907)46:1<22::AID-ANA6>3.0.CO;2-Z

28. Sanghera MK, Grossman RG, Kalhorn CG, Hamilton WJ, Ondo WG, Jankovic J. Basal ganglia neuronal discharge in primary and secondary dystonia in patients undergoing pallidotomy. *Neurosurgery* 2003;52:1358–70; discussion 1370–133. doi: 10.1227/01.NEU.0000064805.91249.F5