



## Case report

## Failed DBS for palliation of visual problems in a case of oculopalatal tremor

David Wang<sup>a</sup>, Justin Sanchez<sup>b</sup>, Kelly D. Foote<sup>c</sup>, Atchar Sudhyadhom<sup>c</sup>,  
M. Tariq Bhatti<sup>d</sup>, Steven Lewis<sup>c</sup>, Michael S. Okun<sup>a,c,\*</sup>

<sup>a</sup> Department of Neurology, University of Florida Movement Disorders Center, McKnight Brain Institute, Gainesville, FL, USA

<sup>b</sup> Department of Pediatrics, University of Florida, Gainesville, FL, USA

<sup>c</sup> Department of Neurosurgery, University of Florida Movement Disorders Center, McKnight Brain Institute, Gainesville, FL, USA

<sup>d</sup> Department of Ophthalmology, University of Florida, Gainesville, FL, USA

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**Abstract**

**Objective:** To report the results of attempted bilateral red nucleus (RN) deep brain stimulation (DBS) for the palliative treatment of visual problems associated with oculopalatal tremor (OPT).

**Background:** It is hypothesized that OPT results from a defect in the Guillain–Mollaret triangle, a circuit that includes connections with the dentate nucleus, the contralateral red nucleus, and the inferior olive. We present a high functioning patient (an accountant) who underwent a palliative trial of RN region DBS in an approach targeted through the subthalamic nucleus region. The aim was to reduce eye tremor and improve vision through interruption of the pathologically oscillating circuit in the Guillain–Mollaret triangle.

**Methods:** Following informed consent, a patient with OPT (and failure of multiple classes of medication and botulinum toxin therapy) underwent placement of bilateral DBS electrodes within the region of the RN. He underwent preoperative testing and testing after 12 months of continuous stimulation with the device in monopolar, bipolar, low frequency, and high frequency settings.

**Results:** The patient did not demonstrate significant changes in the neurological examination following the procedure and postoperative programming sessions. Eye tremor was monitored pre- and postoperatively by ocular EMG and did not change in frequency. Following the one-year trial, stimulation was discontinued as there were no improvements in vision.

**Conclusion:** DBS for OPT was not clinically effective. There were many potential reasons for failed efficacy including a failure to implant the electrodes deep and medial enough into the target region because of stimulation induced side effects. Other targets within the Guillain–Mollaret circuit (and outside of the circuit) may be more useful, though they may prove to be less safe and even more difficult to access. Better custom designed DBS leads may be needed for such small targets in critical brain regions.

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**Key words:** DBS; Red nucleus; Physiology; Microelectrode recordings; Oculopalatal

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**1. Introduction**

Oculopalatal tremor (OPT), first described over 100 years ago as oculopalatal myoclonus [1], often presents as pendular

nystagmus associated with a palatal tremor. Secondary cases of OPT typically follow acute brainstem lesions or vascular events [2]. Most reported cases involve continuous palatal tremor in association with vertical pendular nystagmus, though notable variations may include monocular, horizontal or torsional nystagmus, as well as involvement of other branchial-derived muscles [2]. The palliative treatment of visual problems associated with OPT by targeting red nucleus (RN) with DBS has not been previously explored. We present the case of a patient with OPT who had bilateral RN region

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\* Corresponding author. Department of Neurology, University of Florida Movement Disorders Center, McKnight Brain Institute, 100S Newell Drive, L3-100, Gainesville, FL 32610, USA. Tel.: +1 352 273 5550; fax: +1 352 273 5575.

E-mail address: okun@neurology.ufl.edu (M.S. Okun).

DBS through an approach similar to STN DBS for Parkinson disease. The indication for therapy was the palliative treatment of visual difficulties.

## 2. Case report

A 44-year-old man with a history of a pontine cavernous malformation, which was previously surgically resected, presented after awakening with numbness in his hands, diplopia, and a feeling of generalized weakness. Magnetic resonance imaging (MRI) of his head revealed a new pontine hemorrhage. Followup MRI scans showed a persistent cavernous malformation in the pons, and this malformation was extracted by a vascular neurosurgeon.

Following this second surgical resection of the pontine cavernous malformation, the patient progressed with clinical difficulties including swallowing and speech problems. Several weeks later, he re-presented with *Enterobacter* meningitis and required three weeks of treatment with intravenous cefepime. Following the antibiotics, he reported the slow onset and progression of difficulty with vision which he ascribed to abnormal eye movements. He also had poor balance and coordination, persistent diplopia, difficulty swallowing, difficulty speaking due to jerking of his diaphragm, and weakness of all four limbs. Treatment with several types of medications including Gabapentin, Baclofen, Klonopin, Depakote, Meclizine, Primidone, and Levacetam failed to alleviate his visual symptoms. Intra-ocular injections of botulinum toxin A were unsuccessful.

His visual problems resulted in complete disability from his career as a successful certified public accountant. Upon examination, he demonstrated pendular vertical nystagmus at 2.3 Hz and nearly complete limitation of horizontal eye movements. His OPT involved the palate, pharynx, and uvula and the eye movements were synchronized to the ocular tremor. Gait testing revealed a wide-based ataxic walking pattern, truncal ataxia, and inability to perform tandem walking. Additional neurological findings included a mild right hand postural and action tremor, dysmetria on right finger-to-nose testing, but no resting tremor. Characterization of the abnormal findings included a combination of oculo-palato-pharyngeal myoclonus and pendular vertical nystagmus, with occasional diaphragmatic myoclonus.

Despite all medical treatments, his condition was clinically devastating to his quality of life and career as a successful accountant. He was referred to surgical clinic by a neuroophthalmologist for consideration of DBS implantation into the Guillain–Mollaret triangle (either the red nucleus, olive or cerebellum). The red nucleus location was chosen based predominantly on safety and ease of access to the region by utilizing a path similar to the one commonly employed for subthalamic (STN) DBS for Parkinson disease.

The bilateral stereotactic coordinates included an antero-posterior coordinate of 8 mm, a lateral coordinate of 4 mm, and an axial coordinate of 7.5 mm (Fig. 1, Table 1). Micro-electrode recordings were obtained intra-operatively during the procedure. Five cells from the STN and two cells from the red nucleus region were recorded and characterized. Many others cells were encountered, however, we included

only cells with clean physiological characteristics and adequate signal to noise characteristics (2:1 ratio). The average firing rate of the cells was 20 Hz (range 12–27 Hz), with a mean interspike interval of 58 ms. The pattern identified in six of the seven cells using interspike interval histograms was burst-like-skewed, and in one cell tonic. Cells classified as burst-like-skewed demonstrated ISI histograms with two distributions, a Poisson distribution with short interspike frequency, and a skewed quasi-normal distribution representing bursting frequency. When bipolar test stimulation was applied 2-mm dorsal to the planned depth (0– cathodal, 1+ anodal, 135 Hz, 90  $\mu$ s), the patient experienced unacceptable discomfort, including an electric sensation and sweating. Further testing on more dorsal contacts resulted in more adverse effects including sensations of magnetization, shakiness, dizziness, coldness, anxiety, and extreme discomfort. The DBS lead was retracted/adjusted to a more lateral and dorsal position than intended on the left, and more dorsal on the right (Table 1).

The patient was stable following the procedure and exhibited no change in neurological examination, notably denying weakness, numbness, changes in vision, and speech. He did, however, note that his swallowing was worse, and he felt he had mildly worsened balance. Postoperative programming in monopolar, bipolar, low frequency, and high frequency failed to elicit any objective improvement (multiple adjustments over 12 months). The eye tremor was followed pre- and postoperatively by EEG with ocular leads and videotaped analysis. There was no change in frequency, and only mild subjective improvement in amplitude. There was no change in vision. His hand tremor improved slightly, his gait slightly worsened, and his swallowing worsened. Stimulation was subsequently discontinued following the one-year trial (devices switched off and then explanted).

## 3. Discussion

Our attempt to regularize red nucleus firing through DBS failed to produce successful results in attenuating the OPT. This negative result may have been due to several factors, the most important being the side effects encountered when attempting to place the electrode into the RN region. The final measured coordinates of lead placement were discrepant from the planned coordinates mainly because of intraoperative adjustments due to patient discomfort. The dorsal and lateral placement and failure to place a lead within the red nucleus leave in doubt whether direct RN DBS can benefit OPT. Better technology (i.e. a smaller custom made lead) may in the future allow us to directly target the RN, the olive, the dentate nucleus, or other technically challenging regions.

The olivocerebellar rhythmicity in animal models [3] has provided a rationale for choosing the location of DBS placement in human OPT. Administration of harmaline in animal models previously resulted in widespread and sustained olivocerebellar oscillations, which were reported to be transmitted to the contralateral cerebellum and in turn have influence in motor neurons through bulbospinal pathways. This mechanism is believed to be responsible for the genesis of tremor. Further animal studies have revealed that ethanol and diazepam

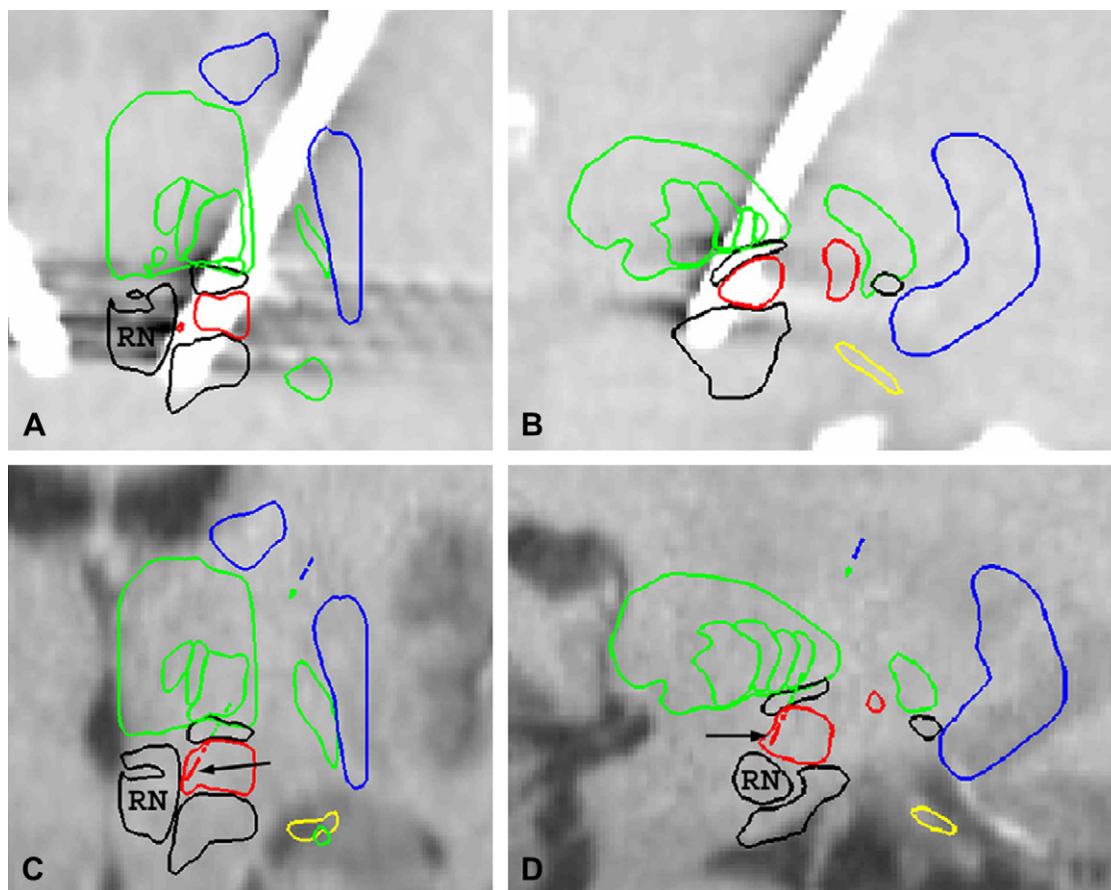


Fig. 1. Atlas overlay of the left approach to the red nucleus “region” with markers of microelectrode recording (dots). The lead was dorsal and lateral to its target (pictured above and coordinates in Table 1). The structures of the basal ganglia (from a morphed three dimensional atlas) are outlined and overlaid on a postoperative CT (A and B) and preoperative MR (C and D) images that have been sliced at angles and positions corresponding to those of the left stimulating electrode and microelectrode. Panel A is a para-coronal slice and Panel B is a para-sagittal slice of a postoperative CT. Panels C and D show a para-coronal and sagittal view of the microelectrode data acquired intra-operatively. The final position of the left stimulating electrode, according to atlas structure positions, is lateral to the red nucleus (altered based on side effects experienced by the patient). The arrows (C and D) indicate the location of the cells that were further analyzed in this paper (left track cells). The structure colors (from superior to inferior) given by thalamus and thalamic nuclei are coded green on the figure (center left), zona incerta is black (under thalamus and above STN), subthalamic nucleus is red (under zona incerta and it has red recording dots within it), red nucleus is black (pictured to the left of subthalamic nucleus), substantia nigra is black (underneath subthalamic nucleus), striatum is blue, globus pallidus externa is green, globus pallidus interna is red (these structures are seen best in panels B and D on the far right of the picture), anterior commissure is black, and optic tract is yellow (also seen best on the far right of panels B and D). This figure reveals a suboptimal location relative to the red nucleus (RN).

suppressed harmaline tremor, suggesting that tremor suppression may result from decoupling of the olivary rhythmicity from other parts of the motor system [4]. Therefore, if DBS could in some way decouple or disrupt this abnormal circuit, it may have the potential to improve symptoms of OPT.

The results of animal studies have thus suggested several targets for treatment of OPT [3,4]. Theoretically, targeting the RN,

dentate nucleus, or the inferior olivary nucleus may result in disrupting and/or decoupling the pathological rhythmicity in this syndrome. The inferior olivary nucleus and dentate nucleus are, however, more difficult to implant than RN. The red nucleus region was chosen in our case mainly based on safety and accessibility, and the failure in outcome may thus have been due to target specificity and technical limitations. We hope by publishing this case that the lessons we learned from the failure can help others in further developing this therapy.

Table 1

Coordinates for planned lead placement compared to final measured coordinates of the DBS leads

	Antero-posterior	Lateral	Axial
Planned target left	−8.0	−4.0	−7.5
Final measured left	−8.0	−9.1	−4.8
Planned target right	−8.0	4.0	−7.5
Final measured right	−7.3	4.8	−4.8

The units of the numbers are represented in millimeters.

Leads were adjusted intra-operatively due to side effects during macrostimulation. Lead was moved dorsal and lateral to limit side effects.

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