HHS Public Access

Author manuscript

Acta Neurochir (Wien). Author manuscript; available in PMC 2020 February 03.

Published in final edited form as:

Acta Neurochir (Wien). 2017 May ; 159(5): 789–793. doi:10.1007/s00701-017-3143-y.

Deep brain stimulation of the centromedian thalamic nucleus for essential tremor: a case report

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Abstract

The centromedian nucleus (CM) of the thalamus is an important site with anatomical connections to different cortical and subcortical motor areas; however, its role in tremor disorders is not clear, although deep brain stimulation (DBS) of the CM has been described to be effective in the treatment of parkinsonian tremor. We report a case of a patient with medication-refractory essential tremor (ET) who had excellent tremor suppression with DBS of the CM. The CM and the nearby region should be explored as a potential target for the treatment of ET and other forms of tremor.

Keywords

Deep brain stimulation; Essential tremor; Centromedian nucleus; Case report

Introduction

The pathophysiology of essential tremor (ET) remains obscure, but most authors consider it to originate from abnormalities in cerebello-thalamocortical connections [7]. High-frequency deep brain stimulation (DBS) is a highly effective treatment option for medication-resistant essential tremor (ET). DBS is usually directed at the ventral intermediate nucleus (Vim) of the thalamus, which receives afferent input from the deep cerebellar nuclei [7]. Recent studies have identified the posterior subthalamic area as an

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Patient consent The patient has consented to submission of this case report to the journal.

Financial disclosures/Conflict of interest None of the authors has any relevant financial or non-financial relationships to disclose.

Comments

This is an interesting case report describing the complexity of surgical treatments of movement disorders. It is well written and the discussion of possible mechanisms of CM having a role in ET is good.

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additional target [14], and, in cases in which ET occurs concomitant with Parkinson's disease (PD), subthalamic nucleus (STN) stimulation [17] may be beneficial. Here we report a case of a patient with medication-refractory ET who had significant and lasting suppression of hand tremor following DBS in the centromedian nucleus of the thalamus (CM).

Case report

A 76-year-old right-handed man with a history of typical ET for over 25 years was evaluated for DBS surgery. He first developed an action tremor in the left hand, followed shortly by involvement of the right hand. Over time, the severity of his hand tremor progressed, and he developed additional mild tremor of the head, voice, and lower extremities. His brother and son had a similar tremor. His past medical history was unremarkable. The hand tremor significantly interfered with activities of daily living, including eating, drinking, writing, and dressing. It was alcohol-responsive, but refractory to commonly used anti-tremor medications, including propranolol, primidone, topiramate, and gabapentin, all given at therapeutic doses. The patient underwent full-body 3D motion analysis with ten high-speed, strobe-synchronized infrared-sensitive digital video cameras (Motion Analysis Corp., Santa Rosa, CA, USA) that were used to track infrared reflecting body surface markers on proximal and distal segments of arms and legs (sampling frequency 120 Hz, spatial accuracy 0.5 mm). Consistent with the diagnosis of ET, spectral analysis of the marker movements showed that the patient had both, a high-amplitude posture-dependent 3.9–4.2-Hz tremor, and a 4.5–5.3-Hz kinetic tremor of lesser amplitude in both arms. The tremor involved both proximal and distal limb, but it was maximal distally. His preoperative Fahn–Tolosa–Marin Tremor rating scale score [5] was 84 (tremor score was 3 in right hand with action and posture). His brain MRI, and neuropsychological and psychiatric evaluations were all normal. Based on these findings, he was considered to be an excellent candidate for DBS surgery targeting the left Vim for right hand tremor.

DBS lead placement was performed using a standard CRW stereotactic head frame (Integra, Plainsboro, New Jersey, USA). A brain MRI was obtained after placement of frame base, determination of the target, and trajectory planning was done using an MRI-guided targeting system (Framelink Software, Medtronic, Minneapolis, MN, USA.) and copied into MRI-based proprietary deformable atlas algorithm for further visualization (Onetrack software developed at Emory University). With an intercommissural distance of 26 mm, the planned trajectory for microelectrode mapping was targeted to the presumed Vim/Vc border at the bottom of the thalamus at 11.5 lateral to third ventricular wall (estimated in coronal and axial planes), 4.5 mm anterior to posterior commissure, and 1 mm below axial midcommissural plane. This yielded target coordinates X = −15, Y = −8.5, Z = −1 relative to midcommissural point (MCP). Intraoperative microelectrode recording and mapping (Axon Guideline System 300, FHC Inc., Bowdoin, ME, USA) was used to guide placement of the DBS lead. Typical thalamic burstneurons [6] were observed throughout the thalamic portion of the trajectory (13-mm span). Limb movement- or tremor-related neurons, however, were not observed, but a thalamic target was identified with a single track where macrostimulation produced significant anti-tremor benefit. This trajectory was used for placement of a DBS lead (Medtronic type 3389, Medtronic, Minneapolis, MN, USA). Intraoperative monopolar

stimulation with the DBS electrode confirmed therapeutic benefit at all contacts, with the lowest threshold for benefit at the lowest contact (C + 0−, 2 V, Pulse width 90 μs, frequency 130 Hz). No sensory or motor side effects were observed with stimulation ofupto5V (pulse width and frequency as stated). The final placement of the electrode was at frame center in the anterior-posterior view, according to fluoroscopic images obtained intraoperatively. There were no perioperative complications. Postoperative MRI done within 24 h showed unexpectedly that the lead was positioned medially and posteriorly to the intended location, at a stereotaxic location corresponding to the CM (Fig. 1), according to the Schaltenbrand and Wahren stereotaxic atlas [18]. The tip of the lead was located at coordinates X = 9.96, Y = −10.71, and Z = 2.88 relative to the MCP. Given that the patient had good intraoperative benefit, the surgical team decided to leave the electrode in place. An implantable pulse generator (Activa SC, Medtronic, Inc.) was placed subcutaneously, below the left clavicle 2 weeks after the lead placement surgery.

When seen 4 weeks post-operatively for initial programming of the IPG, the patient reported that his right hand tremor had worsened contralateral to the implanted lead since the time of the surgery (without stimulation). However, monopolar DBS of the CM contacts (90 μs pulse width, 185 Hz), resulted in substantial reduction of the tremor amplitude contralateral to the stimulation (Fig. 2). At the two lowest contacts of the implanted lead (contacts 0 and 1), the amplitude of tremor was reduced with stimulation voltages above 1.5 V, with an optimal response reached at 3.5 V. At contact 2, improvement first appeared at 3 V, with better control achieved at 4 V, and at contact 3, improvements were seen with 3.5 V stimulation, with better control achieved at 4 V. Stimulation above 4 V was not attempted. The patient did not report sensory or motor side effects. Control of proximal and distal components of the tremor in the right arm was excellent with stimulation at contact 0 (case+, 0−, 3.5 V, 90 μs pulses, 160 Hz). His scores on Fahn–Tolosa–Marin Tremor rating scale scores improved from 84 pre-operatively to 33 postoperatively (tremor scores improved from 3 to 0).

Four months after the initial surgery, a second DBS lead was implanted for left hand tremor, into the right Vim. Postoperative MRI confirmed correct lead placement (coordinates X = 15.3, Y = −4.9, and Z = 2.9 relative to MCP) and the subsequent stimulation with the implanted lead showed the expected good suppression of left hand tremor.

Six weeks after the second surgery for left hand tremor, the patient reported that his right hand tremor had slightly worsened and required adjustment of the voltage on his left IPG to 4.2 V. Two weeks later (approximately 6 months after the first lead implantation), he presented with skin erosion and serosanguinous discharge over the connector located at the level of the left mastoid process. Due to concern for infection along the implanted lead, he underwent surgical removal of the left CM DBS system. After lead removal, tremor in his right hand worsened (Tremor score 3 with action and posture). The right-sided system remains in place, with maintained benefit for left-hand tremor.

Discussion

To our knowledge, this is first report of successful treatment of ET with DBS in or near the CM nucleus. In our case, the patient's response to DBS was noted at all contacts of the implanted lead, with the best control achieved with monopolar stimulation of ventral contacts (0 and 1). We confirmed lead location based on standard atlas coordinates and although there can be heterogeneity in anatomical location, the absence of stimulation-related sensory or motor side effects, even at high stimulation voltages, is consistent with the fact that the lead was placed medially and posteriorly, compared to the intended placement in Vim. It remains unclear how the targeting error arose, but, based on the fact that intraoperative fluoroscopy showed the tip of the lead at frame center, it seems most likely that there was an intraoperative shift of the frame relative to the head (prior to the fluoroscopy).

The posterior intralaminar thalamic nuclear group includes the CM and the parafascicular nucleus (Pf). These nuclei are topographically organized [13, 16]; the CM receives inputs from the 'motor' portion of the basal ganglia and sends somatotopically organized glutamatergic projections to the movement-related portion of the striatum, the putamen. CM also provides a projection to the STN and sparse projections to the motor and premotor cortices. By contrast, Pf receives input from non-motor basal ganglia output nuclei, and primarily projects to the associative/limbic portion of the striatum [13, 16]. Lesioning of the CM has been reported to improve tremor related to cerebellar dysfunction and parkinsonism [1]. In small case series, DBS of the CM/Pf region was shown to provide benefit in controlling levodopa-induced dyskinesia and tremor in parkinsonian and non-parkinsonian patients [4, 9, 12]. In a previous analysis of electrode locations in ET patients treated with thalamic DBS, it was found that leads placed medially near the CM/Pf controlled tremor less efficiently than laterally placed leads closer to Vim [10]. Based on their findings, the authors suggested that CM/Pf DBS may be (partially) effective in the treatment of parkinsonian tremor, but less effective for ET than DBS of Vim [10].

Given the fact that ET is considered to be caused by dysfunction of the cerebellar outflow pathways, the patient's excellent response to tremor with CM DBS was unexpected, because the CM is not known to have substantial direct connections to the cerebellum. Although microlesion effect from lead placement can transiently improve tremor [15], this is less likely to explain the improvement in our patient as he did not benefit from the lead placement (without stimulation), while tremor improved after the start of DBS. Several pathways may have been involved in the anti-tremor effects of CM DBS. It is possible that the CM stimulation directly affected cortical motor areas, bypassing the cerebello-thalamocortical route (see above). It is also possible that the electrical field from the CM stimulation spread to the cerebellar-receiving Vim nucleus and central lateral nucleus (CL) [11] but this is unlikely to be the full explanation for the observed tremor suppression, as the effect was strongest at the most ventral contacts (which are at the greatest distance to Vim and CL), and occurred with relatively low voltages. It is also conceivable that the CM stimulation primarily affected striatal activity, with secondary effects on the STN, and, via the pontine nuclei, the cerebellum [3, 8]. In fact, STN DBS was previously reported to result

in significant tremor suppression in patients with ET [2], although activation of nearby cerebello-thalamic fibers, cannot be ruled out.

Conclusions

Although it remains unclear which pathways were involved in the anti-tremor effects of stimulation of the apparent CM area in this patient, our observation suggests the intriguing possibility that alternate circuits may provide novel targets for tremor control.

Funding sources for study

Thomas Wichmann: The writing of this article was supported by a grant from the NIH/ORIP to the Yerkes Center (P51-0D011132). Mahlon DeLong: received support from APDA for writing this article.

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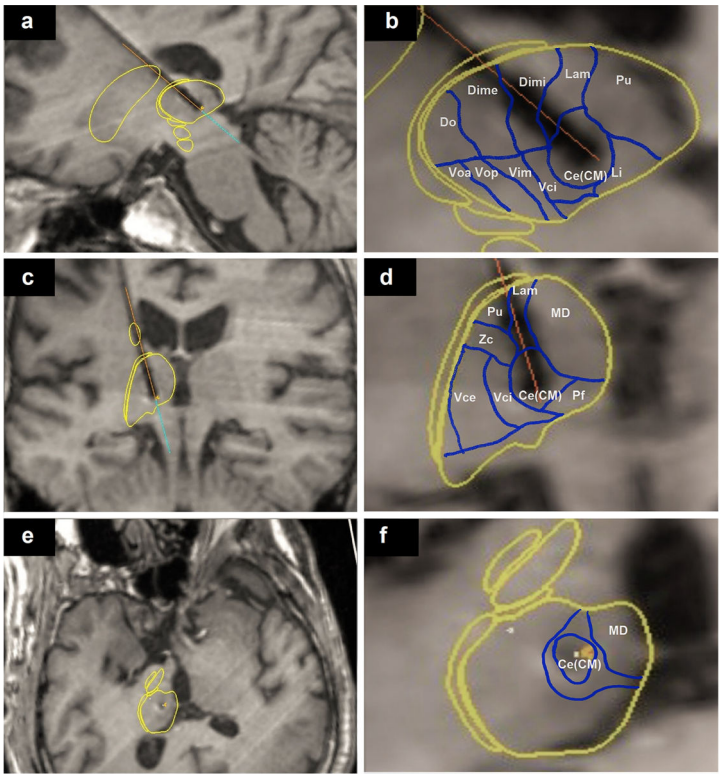

Fig. 1.

Post-operative brain MRI scans with reconstruction of striatal and thalamic boundaries in parasagittal (**a**, **b**), coronal (**c**, **d**), and axial (**e**, **f**) views. The *orange line* demonstrates the trajectory of the DBS lead with its tip extending into the CM (approximate coordinates X = 9.96, Y = −10.71, and Z = 2.88). Images **b, d, f** show the thalamic portion of images **a, c and e**, with a schematic representation of the approximate positions of the different thalamic nuclei, based on the standard neurosurgical atlas by Schaltenbrand and Wahren. *Pu* pulvinar, *Li* nucleus limitans, *Ce* centromedian nucleus, *Pf* parafascicular nucleus, *Lam* nucleus intralaminaris, *Vci* nucleus ventrocaudalis internus, *Vce* nucleus ventrocaudalis externus, *Vim* ventrointermediate nucleus, *Vop* ventro-oralis posterior, *Zc* nucleus zentrocaudalis, *Voa* ventro-oralis anterior, *Do* dorsalis oral nucleus, *Dim* dorsal intermediate nucleus (*i* interna, *e* externa), *MD* median nucleus. For other abbreviations, see text

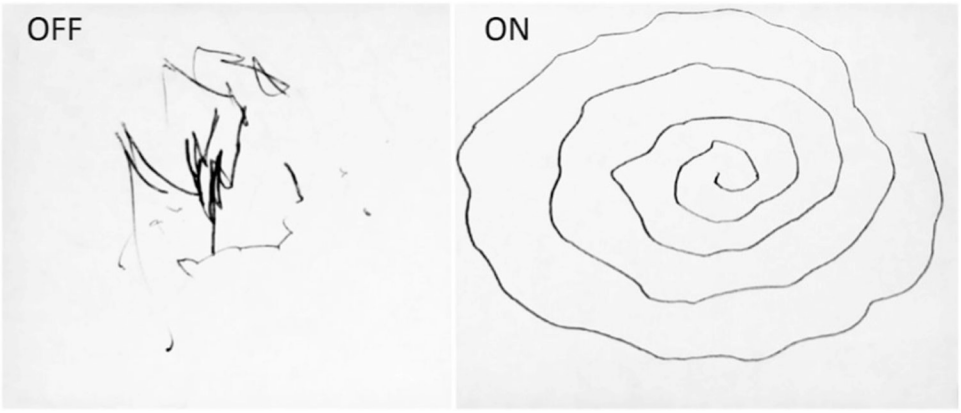

Fig. 2.
Spiral drawing with right hand, OFF and ON DBS stimulation at contact 0 of the DBS lead positioned in the left CM