Journal of the Neurological Sciences 366 (2016) 59–64

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Hyperhidrosis associated with subthalamic deep brain stimulation in Parkinson's disease: Insights into central autonomic functional anatomy

Adolfo Ramirez-Zamora [a,*], Heather Smith [b], Youngwon Youn [b], Jennifer Durphy [a], Damian S. Shin [c], Julie G. Pilitsis [b]

[a] Department of Neurology, Albany Medical College, Albany, NY, United States
[b] Department of Neurosurgery, Albany Medical College, Albany, NY, United States
[c] Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, NY, United States

ARTICLE INFO

Article history:
Received 28 October 2015
Received in revised form 2 April 2016
Accepted 24 April 2016
Available online 26 April 2016

Keywords:
Deep brain stimulation
Autonomic system
Hyperhidrosis
Sweating
Subthalamic nucleus
Zona incerta
Parkinson's disease

ABSTRACT

Introduction: There is limited evidence regarding the precise location and connections of thermoregulatory centers in humans. We present two patients managed with subthalamic nucleus (STN) Deep Brain Stimulation (DBS) for motor fluctuations in PD that developed reproducible hyperhidrosis with high frequency DBS.
Objective: To describe the clinical features and analyze the location of the electrodes leading to autonomic activation in both patients.
Methods: We retrospectively assessed the anatomical localization, electrode programming settings and effects of unilateral STN DBS leading to hyperhidrosis.
Results: Unilateral stimulation of anterior and medially located contacts within the STN and zona incerta (Zi) caused bilateral, consistent, reproducible, and reversible sweating in our patients. Adequate control of motor symptoms without autonomic side effects was accomplished with alternative programming settings.
Conclusion: Stimulation of the medial Zi and medial and anterior STN causes hyperhidrosis in a pattern similar to that described in primates and rats. We speculate that central autonomic fibers originating in the lateral hypothalamic area project laterally to the ventral/medial Zi and then to brainstem nuclei following an medial and posterior trajectory in relationship to STN.

1. Introduction

Thermoregulation is a critical function of the autonomic nervous system. Temperature, vasomotor, and sweating responses are rigidly regulated through a variety of involuntary thermoregulatory responses controlled by brain mechanisms in an orchestrated manner to optimize and maintain the internal thermal environment [1]. Dysfunction of central autonomic pathways at different levels of the neuroaxis may lead to abnormal sweating and/or thermoregulatory responses. Nevertheless, there is limited evidence of regarding the precise location and connections of thermoregulatory centers in humans. Given the challenges of identifying neural tracks in humans, the exact neurological pathways responsible for sweating are not entirely understood. Evidence from animal studies regarding the locations of autonomic tracts suggests that efferent signals from the preoptic hypothalamus travel via the tegmentum of the midbrain, pons and the medullary raphe regions to the intermediolateral cell column of the spinal cord [2].

Subthalamic nucleus (STN) Deep brain stimulation (DBS) has emerged as a therapeutic alternative for patients with refractory motor fluctuations in Parkinson Disease (PD). DBS delivers high frequency stimulation in closely related subcortical structures providing a unique opportunity to learn about the local effects on central nervous system connections. The effects of DBS on motor symptoms are well documented with marked reduction in motor fluctuations and complications in PD [3]. The effects of DBS on non-motor symptoms are less well established; particularly its effects on autonomic function remain unclear. Recording these effects provides a rare opportunity to assess and locate autonomic pathways in humans and the effects of neurostimulation.

In this article, we report two patients treated with STN DBS for motor fluctuations in PD that developed consistent, reproducible hyperhidrosis with high frequency stimulation. We describe their clinical features and analyze the location of the electrodes leading to this rare adverse effect.

2. Clinical presentation

Patients were diagnosed with PD per UK bank research criteria and they were treated with bilateral STN DBS due to severe motor fluctuations associated with advanced PD. Prior to surgery, neither patient

* Corresponding author at: MC-70 Department of Neurology, 47 New Scotland Ave, Albany, NY 12208, United States.
E-mail address: Ramirea@mail.amc.edu (A. Ramirez-Zamora).

http://dx.doi.org/10.1016/j.jns.2016.04.045
0022-510X/

had a history of dysautonomia except for constipation. There was no history of orthostatic hypotension, sweating abnormalities or genitourinary symptoms. Patients had stereotactic placement of bilateral STN DBS electrodes (Medtronic 3389 leads) as previously described without complications [4]. Postoperative coordinates of each DBS electrode are shown in Table 1.

Patient 1 is a 60-year-old man with a past medical history significant for idiopathic PD for 10 years with severe motor fluctuations. Stereotactic surgical planning and targeting with microelectrode recordings were unremarkable. Right STN intraoperative macrostimulation utilizing contact 0 as the cathode and contact 3 as the anode, pulse width (PW) of 60 μs and frequency of 180 Hz produced contralateral paresthesias at low voltages and dysarthria at 8 V. Around 5 V, patient reported lightheadedness and a feeling of "internal warmth". During initial programming session patient developed a feeling of "heat and sweatiness" when activating right STN contact 0 and 1 in unipolar mode (Table 2). Hyperhidrosis was profuse with higher voltages and bilateral, affecting trunk, arms, and face and leg to a lesser extent. At 6 months postoperatively, hyperhidrosis was reproduced with initial electrode settings following the same distribution. Using more laterally and anteriorly located contacts provided excellent control of motor symptoms. At one year follow up his UPDRS-III score "off" medications improved from 31 point to 7.

Patient 2 is a 37-year-old woman with a history of depression, anxiety and a diagnosis of young-onset PD with early motor fluctuations managed with bilateral STN DBS. While performing right STN monopolar review 1 month post-operatively she noted sudden and uncontrollable sweating at 1.5 V when activating contact 2 (Table 2). Sweating increased with higher amplitudes with associated tachycardia and feeling "really hot". Testing contact 3 with similar configuration caused reappearance of hyperhidrosis. Sweating was bilateral and primarily affected upper extremities and torso. At one year follow up, parkinsonism was adequately managed using ventral contacts. Her UPDRS-III score "off" medications improved from 50 to 20.

3. STN stereotactic anatomy

The STN is a small biconvex-shaped nucleus measuring 3 × 8 × 14 mm (coronal/sagittal/axial) in humans densely surrounded by fiber tracts. Its anterior and lateral surface is surrounded by myelinated fibers of the internal capsule. Other fiber systems surrounding the STN include the zona incerta (Zi) (anterodorsomedial to the STN), Forel field H and the lenticular fascicle (H2 field anterodorsal to the STN), and the thalamic fascicle (H1field dorsomedial to the STN). All these anatomical structures are involved in the course of the pallidothalamic bundle. The pallidofugal fibers crossing the internal capsule pass over the dorsal and medial surfaces of the STN, separating it from the dorsomedially placed rostral Zi and more medially the prelemniscal radiation and the red nucleus. Lying posterior to the STN is the caudal or motor (caudal) component of the Zi (cZI), which extends behind the prelemniscal radiation. Ventral to the zona incerta is the substantia nigra [5].

We observed the development of hyperhidrosis during initial DBS programming in both patients with consistently reproduced side effects when specific contacts were activated with only partial motor benefit. Postoperative programming was dictated by side effects and motor response with marked improvement in parkinsonism with alternative programming (Table 2). In patient number 1, despite the noticeably anterior and medial location of DBS lead, successful control of parkinsonism (primarily freezing of gait) was achieved with activation of contact 2 and 3 in interleaved mode. We suspected that stimulation of the pallidofugal fibers (thalamic fasciculus) dictated clinical improvement as multiple series have reported marked benefit with junctional or dorsally and anteriorly located STN contacts [6–9]. In a subset of patients, maximal motor benefit has been reported with active contacts exclusively located in the rostral ZI and pallidofugal fibers [7,10,11]. In patient number 2 management of parkinsonism was accomplished activating lower contacts located within the motor STN.

Table 1
Post-operative DBS contacts coordinates.

Patient 1
Right STN- (X, Y, Z)
• **Contact 0–9.48 mm** *right* to MC, **0.46** *posterior* to MC, **4.20 mm** *inferior* to MC
• **Contact 1–9.88 mm** *right* to MC, **0.83** anterior to MC, **2.61** inferior to MC
• **Contact 2–10.22 mm** *right* to MC, **1.87 mm** *anterior* to MC, **1.39** mm *inferior* to MC
• **Contact 3–10.88 mm** *right* to MC, **3.31 mm** *anterior* to MC, **0.29** mm *superior* to MC
Patient 2
Right STN- (X, Y, Z)
• **Contact 0–8.55 mm** *right* to MC, **2.48 mm** *posterior* to MC, **5.82 mm** *inferior* to MC
• **Contact 1–9.16 mm** *right* to MC, **1.6 mm** *posterior* to MC, **4.50 mm** *inferior* to MC
• **Contact 2–9.76 mm** *right* to MC, **0.39 mm** *posterior* to MC, **2.75 mm** *inferior* to MC
• **Contact 3–10.36 mm** *right* to MC, **0.94 mm** *anterior* to MC, **0.8 mm** *inferior* to MC

Key:
X = Lateral Coordinate.
Y = A-P Coordinate.
Z = Vertical Coordinate.

4. Discussion

The unusual occurrence of reproducible hyperhidrosis in our patients provided a rare chance to study the functional anatomy of autonomic tracts "in vivo" along a unique opportunity to map autonomic pathways close to the stimulation site. Detailed post-operative lead imaging confirmed the precise stereotactic position within the STN of responsible electrodes (Figs. 1 & 2). Contacts causing hyperhidrosis differed between our two patients indicating stimulation of autonomic fibers at different levels of neuroaxis during their descent from the lateral hypothalamus. In patient 1, the responsible contacts were the most ventral contacts located more anterior and medial within the STN compared to initial planning. We suspect activation of autonomic fibers traveling from the hypothalamic paraventricular nucleus as they course medially from a more lateral location above the substantia nigra and medial to STN. This likely represents activation of the autonomic area near the STN cited by Karplus and Kreidl over a century ago in one of the first attempts to identify central autonomic neurons [12].

In patient 2, autonomic activation occurred with the uppermost contacts, which were located more medial compared to initial stereotactic plan. We believe that activation of autonomic tracts at the level of Zi was responsible for sudomotor effects. Importantly, experimental evidence shows that decussation of autonomic descending fibers from lateral hypothalamus follow a segmental pattern rather forming fiber bundles accounting for bilateral effects [13]. The autonomic regulatory mechanisms (cardiovascular, respiratory) are always bilateral [13]. We acknowledge the limitations of this report including the small sample size and lack of post-mortem data but our patients provide further evidence regarding the location of autonomic fibers in relation to STN and the bilateral nature of central autonomic projections confirmed by the development of bilateral, generalized sweating despite of unilateral stimulation. Stereotactic STN electrode positions are typically posterior to MCP. In our patients, post –operative localization of stimulation electrodes revealed an unexpectedly anterior location bilaterally and decisively medial in both leads causing hyperhidrosis. We propose that the aberrant and unintended location of the leads anteriorly and medial within the STN dictated the unusual occurrence of autonomic activation. In animal studies, it has been demonstrated that stimulation of the medial most region of Zi and anterior and medial STN projections from the hypothalamic thermoregulatory centers induces hyperhidrosis, but to the best of our knowledge, this is the first documented