Pallidal stimulation for Holmes tremor: clinical outcomes and single-unit recordings in 4 cases

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OBJECT Holmes tremor (HT) is characterized by irregular, low-frequency (< 4.5 Hz) tremor occurring at rest, with posture, and with certain actions, often affecting proximal muscles. Previous reports have tended to highlight the use of thalamic deep brain stimulation (DBS) in cases of medication-refractory HT. In this study, the authors report the clinical outcome and analysis of single-unit recordings in patients with medication-refractory HT treated with globus pallidus internus (GPI) DBS.

METHODS The authors retrospectively reviewed the medical charts of 4 patients treated with pallidal DBS for medication-refractory HT at the University of California, San Francisco, and San Francisco Veterans Affairs Medical Center. Clinical outcomes were measured at baseline and after surgery using an abbreviated motor-severity Fahn-Tolosa-Marin (FTM) tremor rating scale. Intraoperative microelectrode recordings were performed with patients in the awake state. The neurophysiological characteristics identified in HT were then also compared with characteristics previously described in Parkinson's disease (PD) studied at the authors' institution.

RESULTS The mean percentage improvement in tremor motor severity was 78.87% (range 59.9%–94.4%) as measured using the FTM tremor rating scale, with an average length of follow-up of 33.75 months (range 18–52 months). Twenty-eight GPI neurons were recorded intraoperatively in the resting state and 13 of these were also recorded during contralateral voluntary arm movement. The mean firing rate at rest in HT was 56.2 ± 28.5 Hz, and 63.5 ± 19.4 Hz with action, much lower than the GPI recordings in PD. GPI unit oscillations of 2–8 Hz were prominent in both patients with HT and those with PD, but in HT, unlike PD, these oscillations were not suppressed by voluntary movement.

CONCLUSIONS The efficacy of GPI DBS exceeded that reported in prior studies of ventrolateral thalamus DBS and suggest GPI may be a better target for treating HT. These clinical and neurophysiological findings help illuminate evolving models of HT and highlight the importance of cerebellar–basal ganglia interactions.

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KEY WORDS Holmes tremor; deep brain stimulation; neurophysiology; oscillation; globus pallidus; Parkinson's disease; functional neurosurgery

IN 1904 Gordon Holmes described a syndrome characterized by a low-frequency rest tremor (< 4.5 Hz), which was accentuated by posture and intentional movements.²⁰ Holmes tremor (HT) usually arises 4 weeks to 2 years after an acute brain event. It is characterized by a large and irregular amplitude tremor often affecting predominantly proximal upper extremities. Holmes tremor is the preferred term, as other terms such as rubral or mid-brain tremor are considered to be anatomically misleading because injury to multiple cortical and subcortical areas has been reported to cause HT.⁷ The exact pathophysiology of HT remains unknown, but lesions involve the

cerebello-thalamo-cortical and dentato-rubro-olivary pathways. Superimposed dysfunction in the nigrostriatal pathway may account for the rest tremor component,^{8,45,53} but not all investigators agree on this point.¹⁶ Holmes tremor may arise secondary to cerebral hemorrhage, tumors, cavernomas, infection, multiple sclerosis, or traumatic brain injury.^{5,14,24,26,27,30,32,33,40,41,44,64,67,68} Medical treatment for HT is often unsatisfactory. Several case reports of patients successfully treated with lesioning procedures as well as deep brain stimulation (DBS) have previously been reported (Table 1). Most commonly thalamic (ventralis intermedius nucleus [VIM]) DBS has been used. In a previous publi-

ABBREVIATIONS AC-PC = anterior commissure–posterior commissure; DBS = deep brain stimulation; FTM = Fahn-Tolosa-Marin; GPI = globus pallidus internus; HT = Holmes tremor; PD = Parkinson's disease; STN = subthalamic nucleus; VIM = ventralis intermedius nucleus; VOA = ventral oralis anterior; VOP = ventral oralis posterior.

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cation we reported the use of unilateral globus pallidus internus (GPi) DBS in a patient with HT due to a mid-brain cerebral infarction with a remarkable improvement in functional outcome.³³ In this paper we report the long-term outcomes of 4 patients who underwent GPi DBS for medically refractory HT treated at our institution, as well as pallidal single-unit discharge characteristics.

Methods

We retrospectively reviewed the medical records of 4 patients who underwent GPi DBS for management of intractable HT at the University of California, San Francisco, and San Francisco Veterans Affairs hospital between August 2006 and February 2009. Baseline clinical characteristics were recorded. An abbreviated Fahn-Tolosa-Marin (FTM) scale was used for tremor rating and was the primary outcome measure.¹¹ Tremor scores from the FTM tremor rating scale parts A, B, and C were summed to obtain a single FTM tremor rating scale score at baseline and last follow-up visit. Stimulation was delivered in a monopolar mode in all but 1 patient, and programming was performed using parameters similar to those used for GPi DBS in Parkinson's disease (PD; Table 2).

All patients underwent implantation of DBS leads in the GPi using microelectrode-guided stereotactic surgery.⁵⁷ Prior to recording, all patients were sedated with propofol for placement of the stereotactic frame as well as the surgical incision. Propofol is known to suppress basal ganglia discharge,²³ but is cleared rapidly, and prior studies in PD and dystonia suggest no neuronal effect of propofol following 30–60 minutes of washout time.^{56,58} Propofol was thus stopped 30 or more minutes prior to neuronal recordings. The Medtronic 3387 lead was used in all patients.

Single-Unit Recording and Analysis

Single-unit recordings were obtained using glass-coated platinum/iridium microelectrode electrodes with impedance of 0.4–1.0 mΩ (Microprobe, or FHC). Signals were band-pass filtered (300 Hz to 4 kHz), amplified, played on an audio monitor, displayed on an oscilloscope, and digitized (20-kHz sampling rate) using the Guideline System 3000 or 4000 (FHC) or Microguide system (Alpha Omega). Cells were recorded approximately every 300–800 μm along each trajectory. Pallidal neurons were screened for movement-related activity based on audible changes in the action potential discharge evoked by passive movements of the contralateral limb. The joints tested were the ankle, knee, hip, shoulder, elbow, and wrist. Once a movement-responsive neuron was identified, cell discharge was recorded both during voluntary movements of the related contralateral joint as well as “at rest.” Cells encountered between the internal medullary lamina and the optic tract were considered GPi cells. Digitized spike trains were imported into offline spike-sorting software (Plexon) for discrimination of single populations of action potentials by principal components analysis. Spike times were used to calculate discharge rate, detect oscillations in neuronal discharge, and evaluate the data stream for occurrence of bursting discharge. Neuronal action potentials were only

included in this study if they could be discriminated with a high degree of certainty, as measured by a clear refractory period in the interspike interval histogram (> 3 msec) and if spontaneous activity was recorded for more than 20 seconds. Neurons whose action potential morphology varied with the cardiac cycle were excluded. Analysis was performed using Matlab software (The MathWorks). The quantification of bursting discharge was performed using the Poisson “surprise” method of Legendy and Salcman,^{31,65} with a “surprise” value of 5. Oscillations in the spike train at 2–35 Hz were evaluated using the “global spike shuffling” method.⁴⁷ GPi unit discharge characteristics were compared with findings in patients with PD previously studied at our center.^{35,55} Statistically significant differences between HT and PD were determined using the Mann-Whitney U-test for continuous data and the chi-square or Fisher exact tests for categorical data.

Lead Locations

Electrode location was measured by postoperative MRI, according to published safety guidelines for performing MRI in patients with implanted DBS systems (<http://professional.medtronic.com/pt/neuro/dbs-md/ind/mri-guidelines/#VOe4MsJ0zcs>).⁴⁶ The MR images were computationally reformatted to be orthogonal to the anterior commissure–posterior commissure (AC-PC) line and midsagittal plane⁵⁷ (Framelink software, version 4.1, Medtronic), and lead tip locations were measured with respect to the midcommissural point (Table 2, Fig. 1).

Results

The clinical characteristics of the patients are summarized in Table 2 and Fig. 1. The mean age at the time of surgery was 47 years (range 29–65 years). At last follow-up after chronic unilateral GPi DBS therapy, the FTM tremor rating scale score improved from a mean of 53.25 ± 5.73 points before surgery to a mean of 11.25 ± 8.42 points, reflecting a 78.87% improvement. Mean length of follow-up was 33.7 months (range 18–52 months). The time course of clinical improvements varied among patients but we observed meaningful improvement of tremor within the first 6 months of therapy in all patients. Additionally, patients reported subjective improvement in other activities of daily life and in social and work environments.

Details of stimulation settings are shown in Table 2. No surgical complications occurred in our cohort. Transient stimulation-induced side effects were observed during programming and resolved after adjusting DBS parameters; the most commonly observed were corticospinal and/or corticobulbar side effects. Three of the 4 patients were stimulated in a single monopolar fashion, all with a standard pulse width of 90 μsec and a frequency of 145–185 Hz. A postoperative MR image showing a typical electrode location is shown in Fig. 1 (Case 4).

Case Reports

Case 1

The patient in Case 1 was a 43-year-old man who experienced a midbrain hemorrhage due to a cavernous mal-

TABLE 1. Case reports and series of DBS in patients with HT

Authors & Year	HT Etiology	No. of Patients	Clinical Outcome Scale	Stimulation Target	Outcome	Follow-Up
Kudo et al., 2001	Rt midbrain cavernous malformation	1	None	Bilat VIM	Tremor suppression	Not specified
Pahwa et al., 2002	Midbrain cavernous hemangioma	1	None	Rt VIM	Significant improvement in postural & resting tremor, kinetic component persisted	24 mos
Romannelli et al., 2003	No obvious MRI abnormality	1	UPDRS-tremor subscore	Lt VIM and lt STN	Tremor component improved	2 yrs
Samadani et al., 2003	Left midbrain cavernous angioma	1	Improved speed of specific task, functional disability score of FTM scale	Lt VIM	4-point decrease in functional disability	Not specified
Piette et al., 2004	Pontine tegmental hemorrhage	1	None	Rt VIM	Functional improvement	1.5 yrs
Nikkhah et al., 2004	Rt midbrain infarct	2	Accelerometer & EMG	Rt VIM	Almost complete tremor improvement	7 mos
	Lt AVM w/ midbrain & thalamic hemorrhage			Lt VIM	80% clinical & EMG improvement	6 mos
Foote & Okun, 2005	Posttraumatic	1	TRS & tremor disability scores	2 rt VIM (border VIM/VOP & border VOA/VOP)	Total TRS improvement 37%, disability score improvement 80%	1 yr
Foote et al., 2006	Posttraumatic tremor	3	TRS	2 VIM (border VIM/VOP & border VOA/VOP)	Total TRS improvement of 38.46%, 48.33%, & 66.67%	1 yr, 6 mos, & 8 mos
Diederich et al., 2008	Lt venous angioma pons	2	CGI-Global Improvement	Lt VIM	Substantially ameliorated postural > rest > intention component	7 yrs
	Rt hemiatrophy midbrain			Rt VIM	Postural > rest tremor	5 yrs
Bandt et al., 2008	Lt midbrain cerebral infarction	1	WHIGET Tremor Rating Scale	Lt lenticular fasciculus	Mild intermittent residual tremors	16 mos
Plaha et al., 2008	No obvious MRI abnormality	1	FTM tremor rating scale	Caudal zona incerta	70.2% improvement in total tremor rating scale	1 yr
Peker et al., 2008	Rt thalamic abscess	1	None	Rt VIM	90% improvement	30 mos
Sanborn et al., 2009	Multilobulated, multiseptated brainstem lesion (thalamus/pons)	1	CGI-Global Improvement	Rt VIM	Full tremor suppression at last follow-up	24 mos
Acar et al., 2010	Subarachnoid hemorrhage	1	CGI-Global Improvement	Bilat VIM	Moderate improvement	3 mos
Follett et al., 2014	Motor vehicle accident, encephalomalacia bilateral anterior & inferior frontal & anterior frontal areas, in addition to 2 thalamic lacunes	1	TETRAS	Bilat VIM	Significant tremor reduction	12–18 mos

(continued)

TABLE 1. Case reports and series of DBS in patients with HT (continued)

Authors & Year	HT Etiology	No. of Patients	Clinical Outcome Scale	Stimulation Target	Outcome	Follow-Up
Issar et al., 2013	"Severe diffuse axonal injuries"	5	FTM scale	3 patients received unilat VIM, 1 received bilat VIM, 1 bilat GPi DBS (had dystonic tremor)	14%-36% improvement in tremor rating scale noted in 3 patients w/ VIM	2-3 yrs, but follow-up tremor scales unavailable for 2 patients
Kobayashi et al., 2014	Lesions of cerebellum, mid-brain, or thalamus	4	FTM scale	All 4 patients received dual subthalamic area & thalamic DBS (VO/VIM)	93%-100% improvement in tremor rating scale	2 yrs

AVM = arteriovenous malformation; CGI = Clinical Global Impression; EMG = electromyography; TETRAS = The Essential Tremor Rating Assessment Scale; TRS = Tremor Rating Scale; UPDRS = Unified PD Rating Scale; WHIGET = Washington Heights-Inswood Genetic Study of Essential Tremor.

TABLE 2. Clinical demographics and FTM tremor rating scale scores at baseline and at last clinical follow-up

Case No.	Age at Time of Surgery (yrs)*	Neuroimaging Findings	Pharmacotherapy Trials	FTM Scale Score		Length of Follow-Up (mos)	DBS Programming Parameters† (V/μsec/Hz)	GPi Lead Tip Location (x/y/z [mm])§
				Baseline	Last Follow-Up			
1	43	Rt midbrain hemorrhage from cavernous malformation	Benzodiazepines, pramipexole, carbidopa/levodopa, baclofen	56	23	52	Bipolar: 0 + 1-2.5/90/185‡	19.6/0.34/-5.4
2	65	Multiple lt multicystic midbrain tegmentum lesions	Propranolol, lorazepam, pramipexole, trihexyphenidyl, carbidopa/levodopa	58	10	36	Monopolar: 1-2.8/90/185	19.1/2.5/-5.0
3	29	Lt temporal lobe encephalomalacia & residual lt thalamic bullet fragment	Gabapentin, topiramate, phenytoin	54	3	29	Monopolar: 1-4.5/90/145‡	19.2.1/-6.0
4	50	Rt thalamic/subthalamic infarction	Carbamazepine, trihexyphenidyl, amantadine, olanzapine, quetiapine, clonazepam, reserpine, gabapentin, lamotrigine, botulinum toxin, carbidopa/levodopa	45	9	18	Monopolar: 1-2.0/120/145	19.5/4.0/-7.5
Mean				53.25	11.25	33.75		

* All patients were male.

† Given as voltage (V)/pulse width (msec)/frequency (Hz).

‡ Thalamic leads were "off" after 8 months of multiple programming sessions with lack of additional symptomatic benefit.

§ DBS lead tip locations (in mm) with respect to the midcommissural (AC-PC) point.

FIG. 1. Axial T1-weighted MR images of brain pathology in our patient cohort: multiple tegmental cystic lesions (A), temporal lobectomy and posterior midbrain encephalomalacia (B), and GPI lead location (C).

formation. Approximately 1 month after his stroke, he developed left HT and severe head tremor unresponsive to medical management. He underwent placement of a right thalamic (VIM) DBS lead for tremor control. One month after continuous VIM stimulation the patient reported minimal improvement in his tremor. Subsequently he underwent placement of 2 additional right leads: 1 in the ventral oralis anterior (VOA) thalamic nucleus and 1 in the right GPi. At 2 months postoperatively, the patient reported that his left-hand tremor was controlled with GPi stimulation, even when his VIM stimulator was off. Activation of the VOA lead did not result in further tremor reduction. Three months later, he reported he could now drive a car using his left hand, swing a bat, and pick up marbles individually with his affected hand. Eight months after the GPi/VOA surgery, it was determined that there was no tremor benefit with thalamic stimulation (either VIM or VOA) and only his GPi stimulator was left on. At 4 years follow-up, the patient reported sustained benefit in tremor control, he was still able to drive unassisted, able to hold a cup with his left hand, and cut meat. He notices marked worsening of tremor when his stimulator is turned off. The short-term outcome of this patient has been previously published.³³

Case 2

This patient was a 65-year-old man with no prior medical history who developed insidious-onset gait difficulties, imbalance, tremor, urinary urgency, and incontinence. He noticed continuous right-arm, and to a lesser extent, right-leg tremor at rest and with action. Brain MRI demonstrated the presence of a complex, multiloculated, noncontrast-enhancing cyst in the left midbrain tegmentum extending up to the ipsilateral thalamus with evidence of mild hydrocephalus. A ventriculoperitoneal shunt was placed, with initial improvement of his symptoms, including tremor, but then gradually he developed worsening symptoms again of his right-sided tremor, leading to marked functional disability. No improvement was obtained with pharmacotherapy. Stereotactic surgical aspiration of the midbrain cyst was accomplished without tremor improvement. Pathological examination of the cyst ruled out neoplastic, inflammatory, or infectious etiologies. He

was diagnosed with cystic brainstem degeneration.⁵⁰ His neurological examination was remarkable for proximal, large-amplitude, low-frequency severe tremor at rest, with action and posture. Five years after tremor onset he underwent unilateral GPi DBS. He had an excellent response to stimulation 2 months postoperatively. He noticed almost complete tremor resolution, with only occasional exacerbations associated with stress, not interfering with daily activities. He was able to drink from a cup using only 1 hand, able to write legibly with minimal assistance, button clothing, open mail, and hold reading material (Video 1).

VIDEO 1. Clip showing tremor examination before and with pallidal DBS in 1 of our 4 patients with HT. Copyright Jill L. Ostrem. Published with permission. [Click here to view with Media Player.](#) [Click here to view with Quicktime.](#)

Case 3

This patient was a 29-year-old right-handed man with a history of traumatic brain injury secondary to an occipital gunshot injury at the age of 17. He underwent surgical debridement of occipital bone fragments, followed by an excellent recovery with resolution of initial motor and sensory deficits. He developed slowly progressive and functionally debilitating kinetic, postural, and rest tremor in his right hand. His neurological examination revealed right upper extremity HT. He had great difficulty writing with his dominant hand and was unable to drink from a cup, cut food, or button his shirt. A head CT scan showed bullet fragments and encephalomalacia in the left temporal region and a small hyperdensity in the left thalamus, likely representing a small bullet fragment. The patient underwent stereotactic placement of 2 DBS leads, 1 in the left GPi and 1 in the left VIM thalamus. His tremor almost completely disappeared once stable GPi stimulation parameters were achieved. Independent thalamic DBS resulted in only minor improvement in the postural component. When thalamic stimulation was added to pallidal stimulation, there was no additional tremor control beyond using GPi alone. For this reason, only the GPi lead has been used for chronic neuromodulation. He reported almost no observable tremor in any position, with no limitations in activities of daily living. He is able to write legibly,

hold his baby confidently, and drink liquids with 1 hand. He was able to return to work as a handyman 6 months after surgery.

Case 4

This patient was a 50-year-old man with a history of complex partial seizures who underwent right anterior temporal lobectomy in 1997 complicated by a right posterior cerebral artery infarction. Approximately 8 months after surgery, he developed slowly progressive involuntary movements involving his left upper extremity, consisting of left-arm coarse resting and kinetic tremor, associated with intermittent choreiform movements. He reported abnormal sustained hand postures, triggered by specific hand positions suggestive of focal limb dystonia. His neurological examination demonstrated a distal and proximal left upper extremity, low-frequency, high-amplitude, coarse, resting, postural, and kinetic tremor. Brain MRI showed postsurgical changes from the prior right temporal lobectomy, and a right parietooccipital and right posterior thalamic and subthalamic area of encephalomalacia consistent with his history of a prior right posterior cerebral artery stroke. The patient underwent unilateral right GPi DBS placement. Initial programming in monopolar mode resulted in partial improvement of his hyperkinetic movements 5 weeks after surgery. He obtained almost complete control of his symptoms and improvement in limb function after optimal neuromodulation parameters were achieved. He has regained skilled use of his hand. He is able to hold and drink from a cup, tie his shoes, cut his food, and use keys normally.

Neurophysiological Findings

Twenty-eight GPi neurons recorded in the resting state were analyzed and 13 of these were also analyzed during contralateral voluntary arm movement. Example recordings and their power spectra are shown in Fig. 2, and neuronal discharge data are summarized in Table 3. The mean firing rate in HT was 56.2 ± 28.5 Hz at rest, and 63.5 ± 19.4

Hz with action. The mean firing rate in HT was significantly lower than that for a PD patient cohort recorded and analyzed with identical techniques at our institution ($p < 0.001$). Bursting discharge was prominent in both HT and PD, but quantitatively greater in HT. Of note, the frequency of spike discharge within identified bursts was higher in PD, consistent with the recently published finding that elevated intraburst discharge rate is one of the most sensitive markers of the parkinsonian state.⁵¹ Neuronal oscillations at or near tremor frequency (2–8 Hz) were prominent in both HT and PD in the resting state (no voluntary movement). The major distinguishing feature of oscillatory discharge in HT was its persistence during active movement, in contrast to PD, for which movement totally suppresses 2–8 Hz neuronal oscillations (Fig. 2 and Table 3).

Discussion

In this article, we report the long-term outcomes of 4 patients who underwent GPi DBS for medically refractory HT treated at our institution. All patients experienced significant improvement in tremor control, with a mean tremor improvement of 79% at the last follow-up appointment. These results are, in general, superior to those reported for other thalamic surgeries in patients with medically intractable HT.

Prior Surgical Approaches to HT

Holmes tremor may respond to levodopa, trihexyphenidyl, clonazepam, cabergoline, levetiracetam, bromocriptine, and piribedil, as well as zonisamide,^{2,5,12,53,59–61,63} but pharmacotherapy is often unsatisfactory. The success of thalamotomy and chronic thalamic stimulation in essential tremor and parkinsonian tremor led to their application in HT^{6,52} and other uncommon tremors. In contrast to the small VIM lesions that are effective for parkinsonian tremor, HT requires large lesions, which may have significant permanent adverse effects.¹⁹ The effectiveness

FIG. 2. Oscillatory single-unit GPi discharge in HT. Images on the left side represent discharge at rest, while those on the right represent discharges during voluntary continuous self-paced flexion-extension elbow movements. A segment of neuronal discharge is shown at the top, and below it the corresponding power spectrum for the entire recording. Tremor frequency discharge is present during both rest and voluntary movement. PSD = power spectral density.

TABLE 3. Globus pallidus internus single-unit discharge characteristics in HT compared with PD

GPi Single-Unit Discharge Characteristic	At Rest			During Voluntary Movement		
	HT	PD Cohort	p Value†	HT	PD Cohort	p Value†
No. of neurons	28	132		13	23	
Mean firing rate $\pm$ SD (spikes/sec)	56.2 $\pm$ 28.5	94.8 $\pm$ 23.7	< 0.001	63.5 $\pm$ 19.4	102.1 $\pm$ 24.1	< 0.001
Proportion of spikes in bursts	0.11	0.06	< 0.001	0.13	0.04	0.004
Mean intraburst firing rate $\pm$ SD (spikes/sec)	182.4 $\pm$ 63.6	245.3 $\pm$ 46.5	< 0.001	214.7 $\pm$ 47.9	270.4 $\pm$ 43.0	0.008
Proportion of cells w/ significant oscillations (Hz)						
2–35	43%	28%	0.11	46%	9%	0.008
2–8*	43%	27%	0.10	46%	0%	< 0.001
13–35*	4%	3%	0.91	0%	9%	0.29
Median frequency of oscillations between 2 and 35 Hz	4.8%	4.4%	0.49	3.2%	21.4%	0.07

* A unit may have significant oscillations in multiple frequency bands.

† Statistically significant p values (< 0.05) in bold.

of thalamotomy in HT often wanes with time.^{3,27,29} Over the course of weeks to months, despite continuous thalamic stimulation, tremor is often refractory or recurs.^{18,21,62,66} The effectiveness of ventrolateral thalamic DBS in HT remains uncertain due to the limited number of cases, relatively short follow-up, and diverse outcome scales used^{1,13,42,50} (Table 1).

Other targets have been proposed as alternatives to achieve better tremor control, including stimulation with multiple leads. Romanelli et al. performed unilateral stimulation of both the VIM nucleus and the subthalamic nucleus (STN) in a single patient with HT as the resting component was not improved after VIM DBS.⁴⁸ Foote et al. implanted unilateral twin cerebellar receiving area (VIM) and pallidal receiving area (VOA/ventral oralis posterior [VOP]) thalamic DBS leads.¹⁵ Dual thalamic stimulation resulted in significant improvement in tremor scales without rebound after 6 months of follow-up. Thalamic and dorsal or posterior STN DBS has been described in multiple case reports in patients with HT secondary to pontomesencephalic lesions with variable short-term results.^{4,9–11,25,27,29,30,33,34,37–40,43,49,50} Recently Kobayashi et al. reported 2-year outcome with dual thalamic and subthalamic area stimulation in 4 patients with HT, with significant benefit.²⁸

Based on the suboptimal results of thalamic stimulation for HT in the literature and in our own experience, we sought alternative targets for chronic stimulation. We hypothesized that modulation of the basal ganglia outflow pathways (GPi) might be superior to that of thalamic DBS. This concept is supported by 2 case reports showing a beneficial effect of pallidal lesioning on HT.^{17,36} Two of our cases used combined thalamic and GPi DBS, but GPi DBS alone proved to be effective and the thalamic leads were eventually not used, prompting us to implant only GPi leads in the subsequent cases.

Pathophysiology of HT Reconsidered

The major long-term benefit of GPi DBS in HT shown here is consistent with emerging concepts of the connectivity between cerebellar and basal ganglia systems. Although HT was originally conceptualized as a disorder of the cerebellothalamic system, there has recently been

a greater appreciation of the interaction of cerebellar and basal ganglia pathways, especially via thalamostriate connections.²² We propose that this interaction is critical to the genesis of tremor in HT, and that neuromodulation of thalamic targets has been relatively ineffective due to the anatomically dispersed nature of thalamic projections to the striatum,⁵⁴ involving both medial and lateral thalamic nuclei. In addition, some HT cases may have a component of direct basal ganglia damage via involvement of the midbrain substantia nigra compacta. However, the mean pallidal firing rates, as well firing rates within neuronal bursts, were much lower than those of PD and were consistent with nonparkinsonian disorders.⁵⁶ An elevation in basal ganglia output, and in the firing rate within burst discharges, would be expected if nigrostriatal denervation was a major contributor to the pathophysiology of HT.⁵¹

Limitations of the Study

The present study has some limitations. The clinical data were collected in a retrospective nonblinded fashion. The neurophysiological and clinical results presented only include 4 patients. Isolation of single units is challenging due to high neuronal density and periodic loss of unit isolation in synchrony with the cardiac cycle. As a result, the number of stable, well-isolated units recorded from each study participant was small. Given the absence of prior reports of neurophysiological characteristics in HT, however, we believe that these results represents an important contribution to the understanding of this tremor disorder.

Conclusions

Globus pallidus internus DBS provided excellent tremor control in a series of 4 patients with HT of diverse etiologies. The clinical and neurophysiological findings of this study support evolving models of HT that emphasize the interconnectedness between cerebellothalamic and basal ganglia pathways in its pathophysiology.

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Conception and design: Ostrem. Acquisition of data: Kilbane, Ramirez-Zamora, Ryapolova-Webb, Qasim, Glass, Starr. Analysis and interpretation of data: Ostrem, Kilbane, Ramirez-Zamora, Starr. Drafting the article: Kilbane, Ramirez-Zamora. Critically revising the article: Ostrem, Ryapolova-Webb, Qasim, Glass, Starr. Reviewed submitted version of manuscript: Ostrem, Glass, Starr. Approved the final version of the manuscript on behalf of all authors: Ostrem. Statistical analysis: Kilbane, Ramirez-Zamora, Ryapolova-Webb, Qasim, Glass, Starr.

Supplemental Information

Previous Presentation

Part of this work was previously presented in poster form at the American Society for Stereotactic and Functional Neurosurgery in San Francisco, California, in May 2012.

Videos

Video 1, Media Player. http://mfile.akamai.com/21490/wmv/digitalwbc.download.akamai.com/21492/wm.digitalsource-national/jns14-1098_video_1.asx.

Video 1, Quicktime. http://mfile.akamai.com/21488/mov/digitalwbc.download.akamai.com/21492/qt.digitalsource-global/jns14-1098_video_1.mov.

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