Case Report

Post-mortem Findings in Huntington's Deep Brain Stimulation: A Moving Target Due to Atrophy

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Abstract

Background: Deep brain stimulation (DBS) has been shown to be effective for Parkinson's disease, essential tremor, and primary dystonia. However, mixed results have been reported in Huntington's disease (HD).

Case Report: A single case of HD DBS was identified from the University of Florida DBS Brain Tissue Network. The clinical presentation, evolution, surgical planning, DBS parameters, clinical outcomes, and brain pathological changes are summarized.

Discussion: This case of HD DBS revealed that chorea may improve and be sustained. Minimal histopathological changes were noted around the DBS leads. Severe atrophy due to HD likely changed the DBS lead position relative to the internal capsule.

Keywords: Deep brain stimulation, Huntington's disease, atrophy, histopathology, chorea, electrode design

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Introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder characterized by adult onset of symptoms, including cognitive decline, psychiatric changes, and movement disorders including but not limited to chorea, dystonia, rigidity, and/or bradykinesia.[1] There is no cure for HD and many therapeutic options have demonstrated limited efficacy, and some treatments such as dopamine blocking agents may result in unintended side effects.[2,3]

Deep brain stimulation (DBS) is a potentially effective surgical treatment option for select medication-resistant and disabling hyperkinetic HD-related comorbidities (e.g. severe chorea and ballism).[4] We have previously reported two HD cases treated with DBS.[5] The first case had medication-resistant chorea in which the chorea at rest responded reasonably well to bilateral internal globus pallidus (GPi) DBS. The second was a case of young onset HD with familial dystonia who presented with generalized dystonia and showed a poor response to

bilateral GPi DBS. We report in this paper the clinical response to long-term DBS and also the brain histopathological findings from the first case.

Case report

A 33-year-old male presented to our clinic with a 4-year history of chorea and an extensive family history of HD. Our group has previously published details of this case.[5] Here we summarize the information in order to put into context our findings. The patient's speech was minimally dysarthric, he had involuntary vocalizations, and he was diagnosed with vocal tics. He had bilateral chorea and ballism of the upper extremities, clonic movements in the lower extremities, and dystonia in his hands and legs. He was unable to self-feed, sit without restraint, or interact with his daughter as a result of his hyperkinetic movements. The patient's hyperkinetic movements failed to respond to multiple dopamine antagonists including Tetrabenazine 25 mg twice a day, which was prescribed to the patient in 2009, but then discontinued because of a decrease in both alertness and appetite. It was determined that palliative bilateral GPi DBS was reasonable given his relatively preserved cognitive function. This decision was made following consultation with the family and the patient about their keen desire for amelioration of choreic movements. Bilateral GPi DBS was performed followed by implantable pulse generator placement 3 weeks later. At the time of surgery, both DBS leads were placed a minimum of 2–3 mm from the internal capsule.

Post surgery

The patient developed worsening dysphagia immediately after the operation, necessitating percutaneous endoscopic gastrostomy tube placement prior to hospital discharge. His gait worsened; bradykinesia had worsened but chorea was significantly better and chorea at rest was completely resolved. The resulting dysphagia and worsening of gait were probably due to a transient postoperative condition rather than lead location, since symptoms improved with time and did not worsen after the DBS device was turned on. The severity of his persistent movement-induced chorea was significantly reduced in magnitude and ballistic character. He had increased falls and dragging of his right foot prior to activation of the DBS device. Following several difficult postoperative months he improved, except in gait and balance. His follow-up clinical scores are summarized in Table 1. From our previous work, we anticipated a mild worsening of motor scores in later years. The mild worsening of Unified Huntington's Disease Rating Scale (UHDRS) motor assessment observed during follow-up could have been expected due to the natural progression of the disease. Furthermore, the worsening of chorea at the 3-year follow-up was most likely a result of the progression of disease because the chorea did not improve when the DBS device was turned off during clinic visits. Nevertheless, it is important to note that the symptoms did not return to pre-DBS levels.

Imaging and DBS settings

Postoperative images of the lead locations are shown in Figure 1. GPi was targeted, and leads were placed approximately 3 mm lateral to the internal capsule at the most ventral contact and matched microelectrode mapping. Optimal stimulation parameters were reached at 6 months post-lead implantation. At his 1-year follow-up, settings were stable with the exception of increasing stimulation frequency. At the 2-year follow-up, chorea was well controlled and no changes were made to his DBS parameters. During the 3-year follow-up visit because of worsening of chorea and right lower extremity dystonia, variable contacts, amplitude, pulse width, and frequencies were assessed, but motor (pulling) side effects were observed with no additional benefits. DBS settings were returned to his 1-year settings. At the 4-year follow-up, his DBS settings were difficult to modify and the patient was no longer able to care for himself independently due to increased whole-body rigidity. He had significant weight loss and developed a sacral decubitus ulcer. Despite his overall clinical decline, his resting chorea suppression remained controlled.

Neuropathology

The patient prospectively consented at the time of DBS implantation to donate his brain to the UF DBS Brain Tissue Network program. Brain

Table **1.** **Baseline and post-DBS UHDRS assessments**

	Pre-DBS	6 mo.	12 mo.	24 mo.	36 mo.	48 mo.
Motor assessment	80	70	75	39	57	58
Chorea subscore	19	15	10	4	6	6
Behavioral assessment (severity/frequency)	3/3	2/1	7/8	0/0	0/0	0/0
Independence scale	50	50	NA	10	10	10
Functional capacity	4	1	NA	1	1	1
Verbal fluency raw score	NA	6	NA	6	2	2
Functional assessment	5	1	1	1	1	1

Abbreviations: DBS, Deep Brain Stimulation; mo., Months; UHDRS, Unified Huntington's Disease Rating Scale.
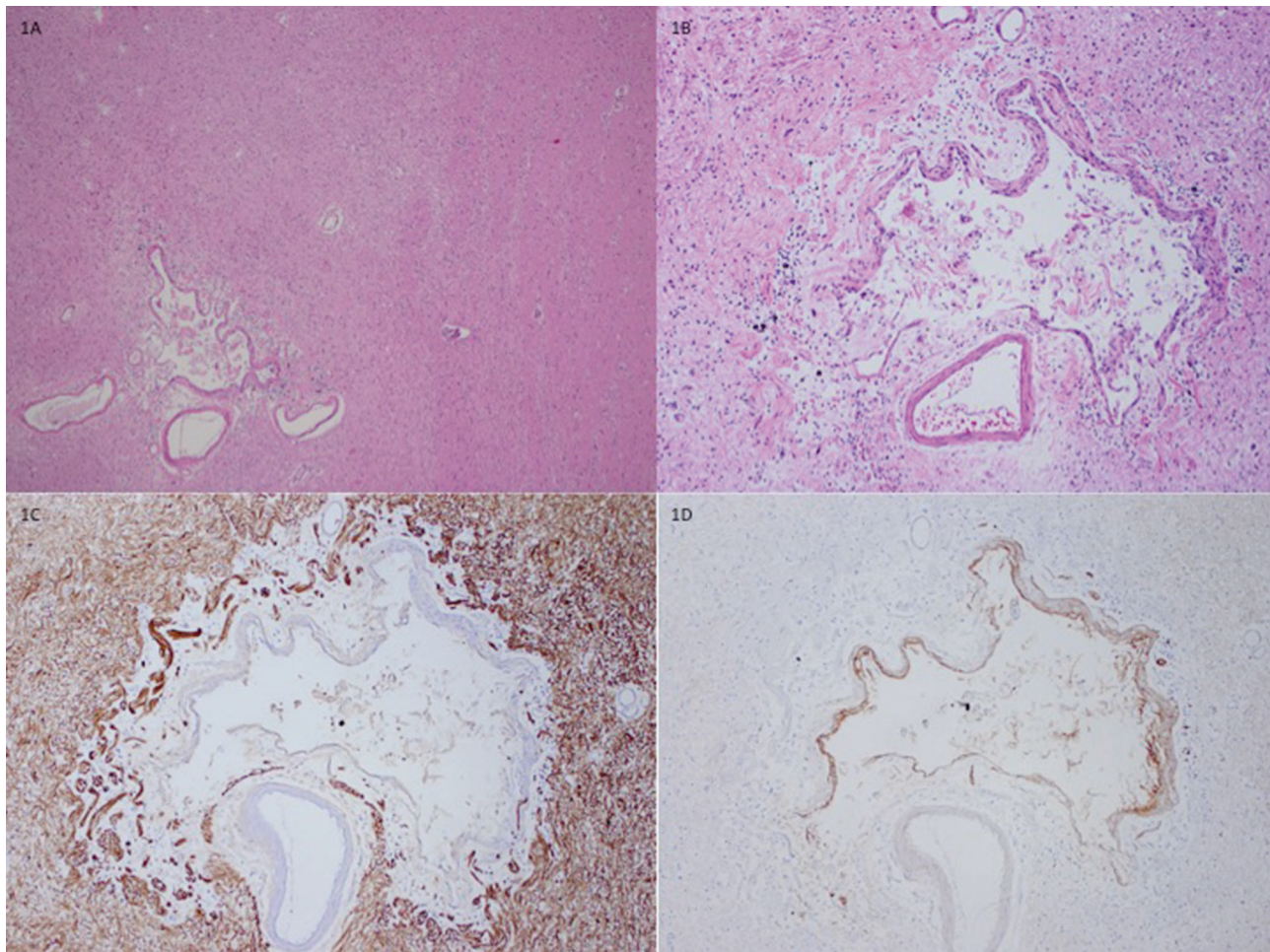
Figure 1. **Microscopic Analysis at the Level of the Tip of the Deep Brain Stimulation Electrode**. (A) The tip of the deep brain stimulation (DBS) lead was placed in the internal globus pallidus (GPi) and was confirmed by postmortem analysis. Progressive atrophy of the GPi resulted in the lead being much closer to the internal capsule (~1.3 mm) than would be predicted by microelectrode mapping and macrostimulation. (B) The tip of a DBS lead placed in the GPi confirmed using hematoxylin and eosin. Some gliosis and hemosiderin deposits are also seen. (C) Gliosis surrounding the tip of the DBS lead as demonstrated by glial fibrillary acidic protein immunohistochemistry. (D) A rim of meningothelial cells near the lead defect as seen by immunohistochemistry using epithelial membrane antigen.

removal was performed within 24 hours of death; the left hemisphere was frozen for other studies and the right hemisphere was fixed in 10% formalin for a follow-up histological examination by a certified neuropathologist (A.T.Y). Samples were taken from the following regions: rostral caudate nucleus, basal ganglia, thalamus, hippocampus, frontal cingulate gyrus and corpus callosum, superior temporal gyrus, midbrain, pons, cerebellum, dentate cerebellum, frontal white matter with DBS tract defect, GPi with distal lead defect, globus pallidus at the anterior commissure, right mesial occipital lobe, and hippocampus. Immunohistochemistry was performed using antibodies to glial fibrillary acidic protein (GFAP) and ubiquitin. The neuropathological burden was stratified on the basis of Vonsattel staging.[7,8]

Gross pathology observations. The cerebral hemisphere revealed mild widening of the gyri and narrowing of the sulci, particularly in the frontoparietal region. There was slight disruption of the cerebral cortex at the site of entry of the DBS lead into the frontal lobe. A 0.4-cm focus of recent subarachnoid hemorrhage was located in the mesial occipital pole adjacent to the primary visual cortex. Serial coronal sections of the cerebral hemispheres revealed marked atrophy of the entire caudate nucleus, resulting in significant hydrocephalus ex vacuo and a marked, straight rather than convex contour of the caudate nucleus, which was atrophied and located adjacent to the lateral ventricle. A small slightly discolored slit-like caudate nucleus was identifiable. DBS lead tracts were followed through serial coronal sections and the distal lead tips were located in the GPi just above the optic track bilaterally. The rostral midbrain, pons, and cerebellum did not reveal any focal lesions.

Microscopic evaluation. Histological examination was performed on the right hemisphere. The caudate nucleus was markedly atrophic and had extensive neuronal loss, gliosis, and significant microglial cell activation. Neuronal loss was also present in the putamen and globus

pallidus, but to a lesser extent. However, reactive astrocytes (GFAP) were abundant in these nuclei. There were rare eosinophilic intranuclear inclusions present in the cerebral cortex; however, no intranuclear ubiquitin-positive inclusions were identified. These findings were consistent with Vonsattel Grade 3 (of 4) for HD staging, indicating that approximately 95% of the neurons in the caudate nucleus were absent. There was focal widening of perivascular spaces within the putamen but no significant atherosclerosis or other vascular pathology within the basal ganglia or deep white matter. There was a

single focus of acute, subarachnoid hemorrhage in the right occipital lobe with abundant hemosiderin-laden macrophages. The cortex adjacent to the subarachnoid hemorrhage revealed subpial gliosis and focal hemosiderosis.

The distal lead tip defect of the DBS electrode was located 1.3 mm from the internal capsule (Figure 2A). There was remote gliosis at the distal tip of the DBS lead as supported by immunohistochemistry for GFAP (Figure 2B), and focal hemosiderin deposition (Figure 2B–H&E, Figure 2C, GFAP). In addition, the lead tip defect was surrounded
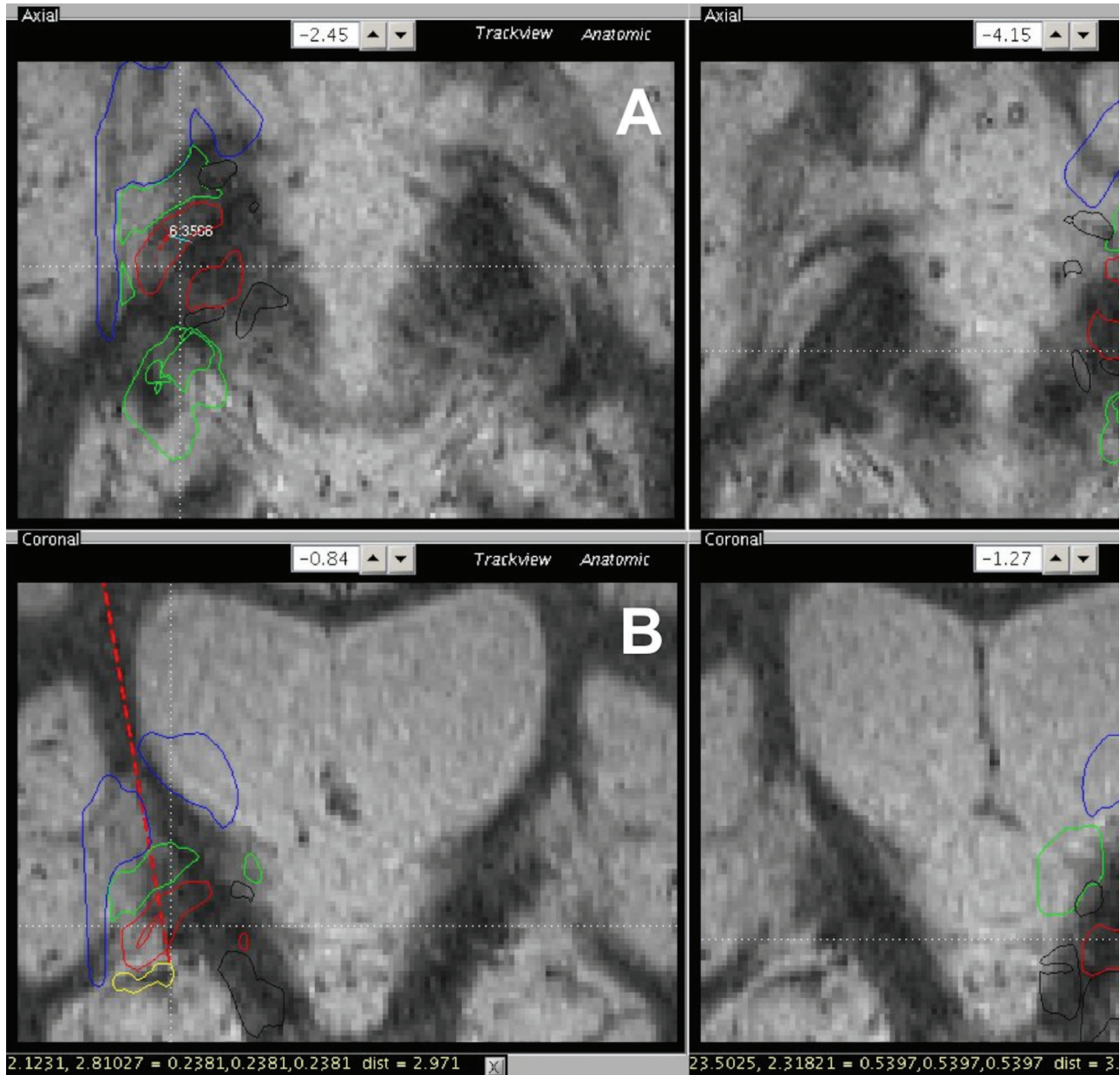

Figure 2. Fusion of Magnetic Resonance and Computed Tomography Images Showing the Lead Locations at the Time of Deep Brain Stimulation Surgery. The deep brain stimulation lead was placed within the internal globus pallidus and was intended to be >2–3 mm away from the internal capsule. The physiology was confirmed by postoperative imaging.

with a "rim" of menigothelial/arachnoidal cells as confirmed by immunohistochemistry for epithelial membrane antigen (Figure 2D). These menigothelial cells could have been derived from perivascular spaces of several small deep penetrating blood vessels that were present near the distal DBS lead tip defect. More proximally along the DBS lead track, in the deep white matter of the right frontal lobe, there was gliosis and hemosiderin deposition. The distal lead tip defect and lead defect in the right frontal white matter show only remote gliosis around a central cavity.

Discussion

This case is the first report in the literature of long-term clinical effects in addition to post-mortem analysis of a HD DBS case. Our patient was followed for several years clinically prior to his death, and this clinical follow-up adds to the importance of the report. Following bilateral GPi DBS, his symptoms were reduced by 51% at 24 months and by 28% at 36 and 48 months as assessed by UHDRS motor scores, with improvements of 79% at 2 years and 68% at 4 years on the chorea subscores. Previously, we had reported the clinical features of this case at 12 months.[5] The patient likely manifested symptoms of disease progression in combination with some minor, stimulation-induced side effects. However, we believe that the change in lead position making it closer to the internal capsule was probably not causing detrimental side effects similar to the effects of the severity of disease progression. As we move towards increasing patient numbers for HD DBS, patient counseling regarding the likelihood of no benefit or worsening of symptoms with disease progression will become an integral part of treatment.

Table **2.** **Reported Cases Using DBS in the Setting of Huntington's Disease**

Study	Patients, n	Target (Bilateral)	Follow-up, months	UHDRS Chorea subscore improvement
Present study	1	GPi	48	68%
Zittel et al.[19]	3	GPi	12–36	40%–58%
Wojtecki et al.[28]	6	GPi and GPe	6	60%
Gonzalez et al.[10]	7	GPi	36	58%
Gruber et al.[15]	1	GPi STN	48	50%
Cislaghi et al.[22]	1	GPi	48	67%
Lopez-Sendon Moreno et al.[20]	1	GPi	60	56%
Huys et al.[11]	1	GPi	12	NA
Velez-Lago et al.[5]	2	GPi	12	73%
Spielberger et al.[21]	1	GPi	48	75%
Garcia-Ruiz et al.[13]	1	GPi	12	NA
Kang et al.[23]	2	GPi	24	50% and 63%
Groiss et al.[18]	1	GPi	NA	NA
Ligot et al.[27]	5	GPe	12–19	NA
Biolsi et al.[14]	1	GPi	48	21%
Fasano et al.[17]	1	GPi	12	77%
Hebb et al.[12]	1	GPi	12	50%
Fawcett et al.[16]	1	GPi	4	56%
Moro et al.[25]	1	GPi	8	64%–76%

Abbreviations: DBS, Deep Brain Stimulation; GPe, External Globus Pallidus; GPi, Internal Globus Pallidus; STN, subthalamic nucleus; UHDRS, Unified Huntington's Disease Rating Scale

Improvements in HD-related hyperkinetic choreic and ballistic movements have been reported by several groups following GPi DBS.[5,10–22] However, several authors have also observed that GPi DBS-induced improvements may not extend to bradykinesia, and this issue has recently been cited as an important limitation of GPi DBS.[10,23–25] This is important to consider in patients similar to the one we have reported. Since our patient was younger than most of the other case reports, a more severe clinical presentation of chorea and/ or rigid-akinetic syndrome could be expected. In such presentations, other targets, which we summarized, could be tried. External globus pallidus (GPe) DBS may, according to the basal ganglia box model,[26] modulate integration of motor symptoms in chorea; however, it remains unknown if GPe DBS will be viable in humans. Two case series of GPe DBS have been recently published, as shown in Table 2.[27,28] In HD patients, during the resting "off" stimulation state, corticosubcortical regional cerebral blood flow has been reported as reduced. In keeping with the basal ganglia thalamocortical circuit model, GPe stimulation may be able to modulate connectivity and reduce regional cerebral blood flow in the basal ganglia and cortical regions.[27] Further support for use of GPe DBS is drawn from the results of a prospective pilot study by Beste et al.,[29] which suggested that GPe stimulation could be regarded as a beneficial treatment, specifically with respect to improvement of cognitive symptoms in HD; however, the rationale for this idea remains speculative.

Postmortem neuropathological examination showed severe atrophy in the caudate nucleus and putamen consistent with the patient's disease stage and consistent with HD progression as shown by several recent studies.[30,31] Microscopic observations and measurement of the distance between the GPi and internal capsule confirmed that when the patient expired, there was a worrisome smaller than expected distance between the internal capsule and GPi, as the DBS lead at death was approximately 1.3 mm away from the internal capsule (Figure 2). Most DBS practitioners prefer approximately 2–3 mm of spacing between the GPi and the internal capsule to avoid stimulation-induced side effects. As globus pallidus atrophy progresses over the course of HD,[30,31] this phenomenon could result in the unintentional realignment of the DBS lead too close to the internal capsule (<2.0 mm), despite adequate placement at the time of implantation. These findings support our previous hypothesis that progressive brain atrophy could affect the long-term outcome of DBS, lead to side effects, and render programming more difficult.[32] However, remarkably in our case, programming could be maintained at similar current densities throughout the 4-year course.

It is possible that smarter DBS devices, such as current steering DBS leads, would be desirable in a situation where atrophy results in increased proximity of adjacent structures to the intended target, resulting in a narrower therapeutic stimulation window.[33] The ideal DBS system would facilitate directional sculpting of the electrical field in order to selectively stimulate the intended target. Novel DBS lead designs may also be specifically relevant for patients whose DBS leads are placed in suboptimal locations, and may present an opportunity for better management of anatomical shifts due to progressive atrophy over time.

In summary, this case revealed that choreic symptoms improve and remain stable following bilateral GPi DBS with a 4-year follow-up. There was improvement of resting chorea and stable improvement in outcome at 48 months post implantation. Despite severe atrophy of the GPi, there was minimal, local histopathological change associated with the DBS device.

References

1. Kim SD, Fung VS. An update on Huntington's disease: from the gene to the clinic. *Curr Opin Neurol* 2014;27:477–483. doi: 10.1097/WCO.0000000000000116.

2. Adam OR, Jankovic J. Symptomatic treatment of Huntington disease. *Neurotherapeutics* 2008;5:181–197. doi: 10.1016/j.nurt.2008.01.008.

3. Shannon KM, Fraint A. Therapeutic advances in Huntington's disease. *Mov Disord* 2015;30:1539–1546. doi: 10.1002/mds.26331.

4. Edwards TC, Zrinzo L, Limousin P, Foltynie T. Deep brain stimulation in the treatment of chorea. *Mov Disord* 2012;27:357–363. doi: 10.1002/mds.23967.

5. Velez-Lago FM, Thompson A, Oyama G, et al. Differential and better response to deep brain stimulation of chorea compared to dystonia in Huntington's disease. *Stereotact Funct Neurosurg* 2013;91:129–133. doi: 10.1159/000341070.

6. Vonsattel JP, Myers RH, Stevens TJ, et al. Neuropathological classification of Huntington's disease. *J Neuropathol Exp Neurol* 1985;44:559–577. doi: 10.1097/00005072-198511000-00003.

7. Vonsattel JP. Huntington disease models and human neuropathology: similarities and differences. *Acta Neuropathol* 2008;115:55–69. doi: 10.1007/s00401-007-0306-6.

8. Gonzalez V, Cif L, Biolsi B, et al. Deep brain stimulation for Huntington's disease: long-term results of a prospective open-label study. *J Neurosurg* 2014;121:114–122. doi: 10.3171/2014.2.JNS131722.

9. Huys D, Bartsch C, Poppe P, et al. Management and outcome of pallidal deep brain stimulation in severe Huntington's disease. *Fortschr Neurol Psychiatr* 2013;81:202–205. doi: 10.1055/s-0033-1335097.

10. Hebb MO, Garcia R, Gaudet P, Mendez IM. Bilateral stimulation of the globus pallidus internus to treat choreathetosis in Huntington's disease: technical case report. *Neurosurgery* 2006;58:E383; discussion E383.

11. Garcia-Ruiz PJ, Ayerbe J, del Val J, Herranz A. Deep brain stimulation in disabling involuntary vocalization associated with Huntington's disease. *Parkinsonism Relat Disord* 2012;18:803–804. doi: 10.1016/j.parkreldis.2012.03.005.

12. Biolsi B, Cif L, Fertit HE, Robles SG, Coubes P. Long-term follow-up of Huntington disease treated by bilateral deep brain stimulation of the internal globus pallidus. *J Neurosurg* 2008;109:130–132. doi: 10.3171/JNS/2008/109/7/0130.

13. Gruber D, Kuhn AA, Schoenecker T, et al. Quadruple deep brain stimulation in Huntington's disease, targeting pallidum and subthalamic nucleus: case report and review of the literature. *J Neural Transm* 2014;121:1303–1312. doi: 10.1007/s00702-014-1201-7.

14. Fawcett AP, Moro E, Lang AE, Lozano AM, Hutchison WD. Pallidal deep brain stimulation influences both reflexive and voluntary saccades in Huntington's disease. *Mov Disord* 2005;20:371–377. doi: 10.1002/mds.20356.

15. Fasano A, Mazzone P, Piano C, et al. GPi-DBS in Huntington's disease: results on motor function and cognition in a 72-year-old case. *Mov Disord* 2008;23:1289–1292. doi: 10.1002/mds.22116.

16. Groiss SJ, Elben S, Reck C, et al. Local field potential oscillations of the globus pallidus in Huntington's disease. *Mov Disord* 2011;26:2577–2578. doi: 10.1002/mds.23914.

17. Zittel S, Moll CK, Gulberti A, et al. Pallidal deep brain stimulation in Huntington's disease. *Parkinsonism Relat Disord* 2015;21:1105–1108. doi: 10.1016/j.parkreldis.2015.06.018.

18. Lopez-Sendon Moreno JL, Garcia-Caldentey J, Regidor I, del Alamo M, Garcia de Yebenes J. A 5-year follow-up of deep brain stimulation in Huntington's disease. *Parkinsonism Relat Disord* 2014;20: 260–261. doi: 10.1016/j.parkreldis.2013.11.007.

19. Spielberger S, Hotter A, Wolf E, et al. Deep brain stimulation in Huntington's disease: a 4-year follow-up case report. *Mov Disord* 2012;27: 806–807; author reply 807–808. doi: 10.1002/mds.24959.

20. Cislaghi G, Capiluppi E, Saleh C, et al. Bilateral globus pallidus stimulation in Westphal variant of Huntington disease. *Neuromodulation* 2014;17: 502–505. doi: 10.1111/ner.12098.

21. Kang GA, Heath S, Rothlind J, Starr PA. Long-term follow-up of pallidal deep brain stimulation in two cases of Huntington's disease. *J Neurol Neurosurg Psychiatry* 2011;82:272–277. doi: 10.1136/jnnp.2009. 202903.

22. Nagel SJ, Machado AG, Gale JT, Lobel DA, Pandya M. Preserving cortico-striatal function: deep brain stimulation in Huntington's disease. *Front Syst Neurosci* 2015;9:32. doi: 10.3389/fnsys.2015.00032.

23. Moro E, Lang AE, Strafella AP, et al. Bilateral globus pallidus stimulation for Huntington's disease. *Ann Neurol* 2004;56:290–294. doi: 10.1002/ana.20183.

24. DeLong MR, Wichmann T. Basal ganglia circuits as targets for neuromodulation in Parkinson disease. *JAMA Neurol* 2015;72:1354–1360. doi: 10.1001/jamaneurol.2015.2397.

25. Ligot N, Krystkowiak P, Simonin C, et al. External globus pallidus stimulation modulates brain connectivity in Huntington's disease. *J Cereb Blood Flow Metab* 2011;31:41–46. doi: 10.1038/jcbfm.2010.186.

26. Wojtecki L, Groiss SJ, Ferrea S, et al. A prospective pilot trial for pallidal deep brain stimulation in Huntington's disease. *Front Neurol* 2015;6:177. doi: 10.3389/fneur.2015.00177.

27. Beste C, Muckschel M, Elben S, et al. Behavioral and neurophysiological evidence for the enhancement of cognitive control under dorsal pallidal deep brain stimulation in Huntington's disease. *Brain Struct Funct* 2015;220: 2441–2448. doi: 10.1007/s00429-014-0805-x.

28. Wakai M, Takahashi A, Hashizume Y. A histometrical study on the globus pallidus in Huntington's disease. *J Neurol Sci* 1993;119:18–27. doi: 10.1016/0022-510X(93)90187-4.

29. Halliday GM, McRitchie DA, Macdonald V, Double KL, Trent RJ, McCusker E. Regional specificity of brain atrophy in Huntington's disease. *Exp Neurol* 1998;154: 663–672. doi: 10.1006/exnr.1998.6919.

30. Martinez-Ramirez D, Morishita T, Zeilman PR, Peng-Chen Z, Foote KD, Okun MS. Atrophy and other potential factors affecting long term deep brain stimulation response: a case series. *PLoS One* 2014;9:e111561. doi: 10.1371/journal.pone.0111561.

31. Martens HC, Toader E, Decre MM, et al. Spatial steering of deep brain stimulation volumes using a novel lead design. *Clin Neurophysiol* 2011;122:558–566. doi: 10.1016/j.clinph.2010.07.026.