Long-term deep brain stimulation for essential tremor: 12-year clinicopathologic follow up.

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ABSTRACT

Purpose: Describe the clinical course and postmortem pathological findings in a patient with essential tremor (ET) treated with deep brain stimulation (DBS) for 12 years.
Methods: This 75 year old woman had a 13-year history of progressive ET prior to implantation of bilateral quadripolar DBS electrodes in her ventral intermediate thalamic nuclei in 1996, producing immediate relief of arm tremor. Detailed histological examination was performed.
Results: Histopathological examination demonstrated electrode catheter tracts rimmed by 20-25 micron fibrous sheaths, with multinucleated giant cells and reactive gliosis. Lymphocytic infiltration was seen by L26 immunoreactivity with CD3 (T cells) staining predominating over CD20 (B cells). Cerebellar axonal spheroids and Purkinje cell loss were found.
Conclusions: Minimal foreign body reaction and gliosis around the electrodes 12 years after implantation supports the long-term safety of DBS. The case represents the longest reported follow-up with autopsy examination after DBS and confirmed histological changes associated with ET.

BACKGROUND

Despite widespread acceptance of deep brain stimulation (DBS) for treatment of neurological disorders for over a quarter century, the long-term effects of electrode implantation and stimulation of human brain have not been well characterized. There is paucity of clinico-pathologic data on patients treated with DBS. We describe the clinical course and postmortem histopathological findings in a patient following 12-year DBS treatment for essential tremor (ET). This case, which represents the longest follow-up of DBS with clinicopathologic analysis, describes brain autopsy findings in ET and provides insights into long-term brain-electrode interactions.

METHODS

The patient was a right handed woman who initially presented at age 63 with left hand tremor while holding objects, with progression to involve the right hand 2 years later. She was diagnosed with ET by a neurologist 9 years after the onset of her tremor, failed to respond adequately to propranolol, primidone, and clonazepam and by 1995, she felt debilitated, experienced difficulty eating and drinking, and was embarrassed by her tremor in public. At age 75, after 13 years of progressive symptoms, she underwent implantation of a quadripolar DBS electrode (Medtronic) into the left ventral intermediate (Vim) thalamic nucleus in January 1996 for her right and dominant sided arm tremor according to previously described method [1].

Left and Right Vim target coordinates are shown in Table 1. (AC-PC line: 25.9 mm). She had marked improvement in her right hand tremor and modest improvement in the left (ipsilateral) hand. Seven months following left DBS implantation, she underwent DBS implantation on the right Vim for left sided tremor.

She experienced excellent control of her ET bilaterally, with the exception of 2 temporary periods of hardware failure including left Vim intracranial electrode fracture at 15 months and a right IPG malfunction in February 1999, both of which were promptly replaced. Stimulation parameter settings remained stable over the 12 year treatment duration, as seen in Table 2.

METHODS - continued

Intracranial Electrode Impedances (ohms wrt case):

Electrode #	Left	Right
0	>2000	1340
1	>2000	1340
2	1400	1284
3	1834	1467

Table 1 shows electrode tip positions intraoperatively and at 11 years, as determined by Brain MRI (June 29, 2007)

Target/Electrode Pos	Initial	Revision	MRI 6/07	Error	x-y RMS
Left Vim	1/26/1996	6/25/1997	6/29/2007		
Lateral (x)	12	12	11.9	-0.1	0.158
A-P (y)	-3	-4	-3.8	0.2	
Vertical (z)	-1	-1	-5.7	-4.7	
Right Vim	8/26/1996		6/29/2007		
Lateral (x)	13		11.3	-1.7	1.33
A-P (y)	-4		-4.8	-0.8	
Vertical (z)	-1		-5.3	-4.3	

Tremor amplitude was at least 75% lower with the DBS turned on compared that with the DBS off. She eventually developed postural instability, confining her to a wheelchair. She developed muscle disuse atrophy, refractory to PT. She died in her sleep on March 29, 2008.

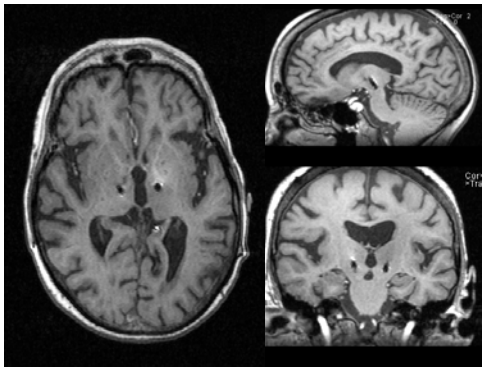

Figure 1: MRI of the Brain 11 years 5 months (06/07) after initial Implantation. Bilateral Vim Electrodes are visible.

Target/Param	Initial	Final
Left Vim	1/26/1996	1/16/2008
Amplitude (v)	2.6	2.5
Frequency (Hz)	120	185
Pulse Width (us)	130	90
Right Vim	8/26/1996	1/16/2008
Amplitude (v)	1.5	2.8
Frequency (Hz)	100	135
Pulse Width (us)	200	60

Table 2: Initial and Final Stimulation Parameters, initially after implantation and at 12 years post-implantation.

RESULTS

The brain was harvested within 12 hours, and its weight was 1200 grams after immersion-fixation for 1 week in 20% formalin. It was carefully sectioned in the coronal plane, tissue blocks were embedded in paraffin, and 4 micron sections were cut and stained. The electrodes were visible entering the surface of the middle gyri in the frontal cortices and terminating in the right thalamus just above the substantia nigra and extending to the left substantia nigra.

RESULTS - continued

Histopathological analysis of the thalami demonstrated fibrous sheaths lining the electrode tracts with thicknesses of 20 and 25 microns on the right and left, respectively. Fibrillary gliosis did not extend beyond 500 microns of the tissue-electrode interface. Reactive astrocytes, characterized by multiple long delicate processes highlighted with GFAP immunostaining, were found bilaterally within 1 mm of the tissue-electrode interface, more on the right. Numerous macrophages (KP-1 immunostain) and some multinucleated giant cells were found bilaterally.

In the implanted thalamic sections, numerous mononuclear leukocytes, highlighted with leukocyte common antigen (LCA), were seen bilaterally. T lymphocytes (CD3 immunoreactive) were more frequently seen than B lymphocytes (L26 immunoreactive). No axonal spheroids, hemorrhage, or perifocal edema were noted on H&E stained sections in the thalami. Patchy loss of cerebellar Purkinje cells was found, with “empty baskets”, associated mild Bergmann’s gliosis, occasional “torpedos” (axonal spheroids of Purkinje cells), and occasional phosphorylated neurofilament protein immunoreactive Purkinje cells (Figure 2).

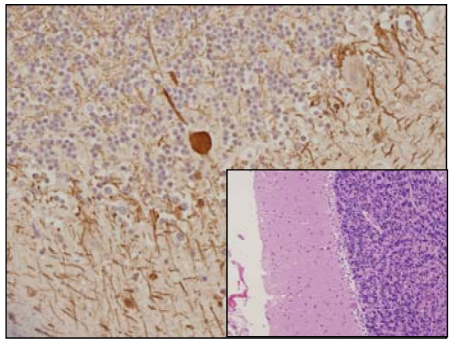

Figure 2: Histopathology of Cerebellum. Large high power image demonstrates a "torpedo" (axonal spheroid), highlighted with neurofilament due to damage to Purkinjie cells; Inset: H&E demonstrating significant loss of Purkinjie cells. Both are nonspecific findings in Essential Tremor.

Feature	Left Thalamus	Right Thalamus
Fibrous Sheath (thickness in microns)	25	20
Fibrillary Gliosis (< 500 microns)	N/A	N/A
Reactive Astrocytosis (< 1 mm)	2	3
Multinucleated Giant Cells	2	2
Mononuclear Leukocytes	3	3
Macrophages	3	3
Microglial Activation	N/A	N/A
Axonal Spheroids	none	none
Fresh Hemorrhage	none	none
Perifocal Edema	none	none

Grading: 1: single, 2: some, 3: numerous

Table 2: Histopathological features of Electrode-Tissue Interface, quantifying fibrotic sheath formation, gliosis, and other cellular reactions in response to electrode implantation in bilateral thalami.

CONCLUSIONS

1. This is the longest follow-up (12-years) of a patient implanted with DBS with postmortem clinicopathologic analysis. The second longest reported follow-up after DBS implantation, reported in 2008, is 6 years [2].
2. Similar to other reports of DBS in ET [3], our patient showed marked reduction not only the contralateral tremor but also realized modest improvement in her ipsilateral tremor [4, 5].
3. Our case is also notable for being the second case in which postmortem analysis was performed on a patient implanted with DBS for ET. The first case, reported in 2000, had a 16-month follow up; however, no neuropathological analysis of the cerebellum was presented in that case [6].
4. The present case adds to the growing literature characterizing neuropathological findings in ET and is the first case in which cerebellar pathology has been analyzed in an ET patient who has undergone DBS implantation.
5. Many aspects of ET, including clinical features, imaging studies, pathological findings, and DBS results point to the cerebellum as playing an important role in the pathophysiology of this disorder.

Despite the high prevalence of ET few patients have been studied at autopsy. Until recently, it was believed that there were no identifiable changes in the brains of patients with ET 12. Cerebellar pathology, however, has recently been described in the brains of patients with ET [7, 8, 9]. In one of the largest clinical-pathological studies, involving 33 ET and 21 control brains, the major cerebellar pathological changes were found to include marked reduction in the number of Purkinje cells and a 7-fold increase in Purkinje cell torpedoes [10].

The neuropathological findings in our case are consistent with the Lewy body negative cerebellar pathology in patients with ET.

6. The case also provides evidence of long-term efficacy and safety of Vim DBS.

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REFERENCES

•1. Kenney C, Simpson R, Hunter C, et al. Short-term and long-term safety of deep brain stimulation in the treatment of movement disorders. J Neurosurg 2007;106(4):621-625.
•2. Guehl D, Vital A, Cuny E, et al. Postmortem proof of effectiveness of zona incerta stimulation in Parkinson disease. Neurology 2008;70(16 Pt 2):1489-1490.
•3. Pahwa R, Lyons KE, Wilkinson SB, et al. Long-term evaluation of deep brain stimulation of the thalamus.[see comment]. J Neurosurg 2006;104(4):506-512.
•4. Ondo W, Dat Vuong K, Almaguer M, Jankovic J, Simpson RK. Thalamic deep brain stimulation: effects on the nontarget limbs. Mov Disord 2001;16(6):1137-1142.
•5. Kovacs N, Pal E, Merkli H, et al. Bilateral effects of unilateral thalamic deep brain stimulation: a case report. Mov Disord 2008;23(2):276-279.
•6. Boockvar JA, Telfeian A, Baltuch GH, et al. Long-term deep brain stimulation in a patient with essential tremor: Clinical response and postmortem correlation with stimulator termination sites in ventral thalamus. Case report. J Neurosurg 2000;93:140-144.
•7. Louis ED, Vonsattel JP, Honig LS, et al. Essential tremor associated with pathologic changes in the cerebellum. Arch Neurol 2006;63(8):1189-1193.
•8. Axelrad JE, Louis ED, Honig LS, et al. Reduced Purkinje cell number in essential tremor: a postmortem study. Arch Neurol 2008;65(1):101-107.
•9. Louis ED, Vonsattel JP. The emerging neuropathology of essential tremor. Mov Disord 2008;23(2):174-182.
•10. Louis ED, Faust PL, Vonsattel JP, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007;130(Pt 12):3297-3307.