An Unusual Inflammatory Response to Implanted Deep Brain Electrodes

Peter S. Hughes, Jerry P. Kreek, Douglas E. Hobson, Marc R. Del Bigio


Since the late 1980s, deep brain stimulation (DBS) has gained increasing popularity in the treatment of movement disorders and other conditions. The U.S. Food and Drug Administration approved DBS of the thalamus for the treatment of Parkinson's disease and essential tremor in 1997, and DBS of the subthalamic nucleus and the globus pallidus internus for patients with Parkinson's disease in 2002. Deep brain stimulation has also found a role in the management of dystonia, Tourette syndrome and obsessive-compulsive disorder. By the end of 2007, more than 55,000 patients worldwide had undergone DBS therapy.

Despite the large number of procedures, fewer than 50 autopsy reports have documented brain changes associated with the electrodes. In general, the placement of DBS electrodes and other types of invasive hardware into brain tissue is thought to induce only minor changes in the surrounding parenchyma, typically consisting of mild astroglial and microglial responses. Here we report the autopsy findings of a man who underwent DBS for treatment of dystonia and at the time of death was found to have dense lymphocyte collections surrounding the electrodes.

CASE DESCRIPTION

This man suffered from a generalized dystonic tremor, principally involving his upper extremities, with mild dystonia in his right leg. The symptoms had begun when he was 12 years old, but had not interfered with his daily activities until he was in his 50s. Two other family members reported similar symptoms. Despite trials of several medications (including propranolol, topiramate, acetazolamide, lorazepam, levodopa and gabapentin), the dystonia and tremor progressed, eventually interfering with eating, writing, and carrying out his work as a farmer. At age 52 years, he underwent placement of a Medtronic Kineta stimulator (Model 7428; Medtronic, Minneapolis MN) with bilateral quadripolar electrodes (Medtronic model 3387) in the ventro-intermediate thalamic nucleus. The stimulating electrodes are platinum-iridium and the wire leads are coated with 90A urethane5, which is a polyurethane/methylene glycol-based polyurethane elastomer coated with dibutyltin dilaurate. He reported a substantial improvement in his tremor and dysarthria, and was able to function without any medication. During the entire treatment period the active electrodes bilaterally were the proximal (+) and penultimate proximal (-) electrodes. The initial parameters were pulse width (60μsec), rate (3,030Hz), impedance (right 614 ohms and left 793 ohms), and current (right 70μA and left 35μA). Two years later the rate was increased to 160Hz and the right side current was increased to 105μA. One year later the left side current was increased to 70μA. Ten months prior to death the settings were restored to the original levels; at that time impedance was ~1050 ohms bilaterally. Two months later (eight months prior to death), the impedance returned stable. Shortly thereafter the battery was replaced without complication. Seven months later, at the age of 56 years, the man collapsed and could not be resuscitated from ventricular fibrillation. No neurological changes had been reported in the months prior to death. The autopsy revealed a single focus of active microglia and multiple foci of myocellular fibrosis consistent with healed microglia, which may have caused an arthrythmia. Myocarditis due to viral infection is a well-recognized cause of sudden death.

For the electrode wires entering the frontal lobes, the brain (1.5kg) was grossly normal. Coronal sections through the cerebral hemispheres confirmed the electrode position within both thalami, terminating at the upper margin of the subthalamic nucleus (Figure A). Microscopic examination of brain tissue surrounding the lead paths showed mild loss of neurons, a thin collagen sheath, rare reactive astrocytes (demonstrated by glial fibrillary acidic protein (GFAP) immunostaining), and small collections of perivascular lymphocytes. Along the middle one cm of the right electrode array, likely corresponding to both active and inactive electrodes, multiple foci of perivascular lymphocytes were present. There were no multinucleate giant cells and no refractive material evident on polarized illumination. In the left thalamus a 1.5cm electrode array site was evident. Inflammation was most prominent in the dorsal region, corresponding to active electrode sites (Figure B). On polarized illumination very rare multi-nucleate giant cells with streaks of refractile material (possibly polyurethane debris) were identified near the electrode tip in the ventral thalami. These cells were surrounded by collagen with no lymphocytes in the immediate vicinity (Figure C). Immunostaining showed roughly equal and intermingled populations of CD3 positive T-lymphocytes (CD4 greater than CD8) and CD20 immunoreactive B-lymphocytes. Immunostaining for human leukocyte antigen (HLA-DR) demonstrated rare monocytes among the lymphocytes and suggested that the damage depends on the electrode material (e.g. stainless steel is more irritating than platinum-iridium) and possibly the charge density.

Autopsies have been reported on fewer than 50 human subjects who died with DBS electrodes in place. These have revealed histological changes similar to those reported in the animal models. The largest study documented findings in the brains of eight Parkinson's disease patients whose electrodes had been operating for up to 70 months. Mild reactive astroglia was evident around the electrode lead tracks, but the surrounding neural parenchyma was well preserved. In two of the cases there was slight microglial activation and rare ("foreign body type") multinucleate giant cells. A review of 37 published autopsies, as well as single case reports not covered in the review, documented comparable features as well as collagenous encapsulation of the wire track. Only scattered lymphocytes in the vicinity of the electrode tracks have been reported. In addition to the case reported here, we have examined an autopsy case of a 73-year-old man with Parkinson disease in whose tremor was treated with bilateral subthalamus stimulators for four years. The minor histological changes were similar to those previously reported in literature. One post-mortem study used electron microscopy to examine fragments of brain tissue attached to 21 explanted DBS electrodes. The authors speculated that electron-dense inclusions in microglia were fragments of polyurethane.

This case stands out from previously published cases because of the intense lymphocytic infiltration at the electrode sites. These were several possible explanations for this. First, this might simply represent an extreme of the body's response to platinum-iridium electrodes or polyurethane degradation products.

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Figure A. Photograph of coronal section through left thalamus showing electrode tracks. The two most dorsal electrodes were the active ones (green), the left side, C. Photomicrograph (hematoxylin and eosin stained section, polarized light) showing a multinucleate giant cell that contains refractile material (arrows). There are no lymphocytes in the immediate vicinity of this cell, which was near the ventral electrode tip. Bar = 40μm for B and 20μm for C.
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Despite the large number of procedures, fewer than 50 autopsy reports have documented brain changes associated with the electrodes. In general, the placement of DBS electrodes and other types of invasive hardware into brain tissue is thought to induce only minor changes in the surrounding parenchyma, typically consisting of mild astrocytosis and microglial responses.

Here we report the autopsy findings of a man who underwent DBS for treatment of dystonia and at the time of death was found to have dense lymphocyte collections surrounding the electrodes.

CASE DESCRIPTION

This man suffered from a generalized dystonic tremor, principally involving his upper extremities, with mild dystonia in his right leg. The symptoms had begun when he was 12 years old, but had not interfered with his daily activities until he was in his 30s. Two other family members reported similar symptoms. Despite trials of several medications (including propranolol, topiramate, acetazolamide, lorazepam, levodopa and gabapentin), the dystonia and tremor progressed, eventually interfering with eating, writing, and carrying out his work as a farmer. At age 52 years, he underwent placement of a Medtronic Kinnetra stimulator (Model 7428; Medtronic, Minneapolis MN) with bilateral quadripolar electrodes (Medtronic model 3387) in the ventro-intermediate thalamic nucleus. The stimulating electrodes are platinum-iridium and the wire leads are coated with 90A ethane, which is a polytetrafluoroethylene-based polyurethane elastomer coated with dibutyltin dilaurate. He reported a substantial improvement in his tremor and dystonia, and was able to function without any medication. During the entire treatment period the active electrodes bilaterally were the proximal (+) and penultimate proximal (-) electrodes. The initial parameters were pulse width (60μsec), rate (3,036Hz), impedance (right 614 ohms and left 793 ohms), and current (right 70μA and left 35μA). Two years later the rate was increased to 160Hz and the right side current was increased to 105μA. One year later the left side current was increased to 70μA. Ten months prior to death the settings were restored to the original levels; at that time, impedance was 1,050 ohms bilaterally. Two months later (eight months prior to death), the impedance remained stable. Shortly thereafter the battery was replaced without complication. Seven months later, at the age of 56 years, the man collapsed and could not be resuscitated from ventricular fibrillation. No neurological changes had been reported in the months prior to death. The autopsy revealed a single focus of active myocarditis and multiple foci of myocardial fibrosis consistent with healed myocarditis, which may have caused an arrhythmia. Myocarditis due to viral infection is a well-recognized cause of sudden death.

Except for the electrode wires entering the frontal lobes, the brain (1,545 g) was grossly normal. Coronal sections through the cerebral hemispheres confirmed the electrode position within both thalami, terminating at the upper margin of the subthalamic nuclei (Figure A). Microscopic examination of brain tissue surrounding the lead paths showed mild loss of neurons, a thin collagen sheath, rare reactive astrocytes (demonstrated by glial fibrillary acidic protein (GFAP) immunostaining), and small collections of perivascular lymphocytes. Along the midline one cm from the right electrode array, likely corresponding to both active and inactive electrodes, multiple foci of perivascular lymphocytes were present. There were no multinucleate giant cells and no refractile material evident on polarized illumination. In the left thalamus a 1.5 cm electrode array site was evident. Inflammation was most prominent in the dorsal region, corresponding to active electrode sites (Figure B). On polarized illumination very rare multi-nucleate giant cells with streaks of refractile material (possibly polyurethane debris) were identified near the electrode tip in the ventral thalami. These cells were surrounded by collagen with no lymphocytes in the immediate vicinity (Figure C). Immunostaining showed roughly equal and intermingled populations of CD3 positive T-lymphocytes (CD4 greater than CD8) and CD20 immunoreactive B-lymphocytes. Immunostaining for human leukocyte antigen (HLA-ABC) demonstrated rare monocytes among the lymphocytes and microglial activation extending >300 microns beyond the electrodes. Inflammation was negligible along the wire path. There was no evidence for meningitis or generalized encephalitis except for a single small focus of perivascular lymphocytes in the right caudate nucleus head. There was no microscopic evidence of disease that would explain the dystonia and tremor.

DISCUSSION

The perioperative risks associated with DBS are well documented, and include intracranial hemorrhage and infection at the implantation site. Less clear, however, is the way in which brain tissue responds to chronically implanted hardware. Tissue reaction to stimulating electrodes could impair current delivery into the surrounding brain tissue. The cellular mechanisms through which brain tissue responds to the introduction of a foreign body and the manner of electrode 'biocompatibility' have been reviewed. Several animal studies have demonstrated that electrodes chronically implanted into brain tissue induce a transient localized microglial reaction. This is accompanied by a more sustained microglial reaction, which leads to the formation of an "insulating" sheath around the foreign body. A chronic inflammatory response may be the driving force behind these histological changes, and it appears that the effect is related to the presence of a foreign body, rather than the trauma associated with electrode insertion. Continuously active electrodes appear to cause a more marked reaction than intermittently active electrodes or electrodes through which no current is passed. A few experimental reports caution that focal necrosis can occur with the application of an unbalanced monophasic current. Other animal studies have suggested that the damage depends on the electrode material (e.g., stainless steel is more irritating than platinum-iridium) and possibly the charge density.

Autopsies have been reported on fewer than 50 human subjects who died with DBS electrodes in place. These have revealed histological changes similar to those reported in the animal models. The largest study documented findings in the brains of eight Parkinson’s disease patients whose electrodes had been operating for up to 70 months. Mild reactive astrogliosis was evident around the electrode lead tracks, but the surrounding neural parenchyma was well preserved. In two of the cases there was slight microglial activation and rare ("foreign body type") multinucleate giant cells. A review of 37 published autopsy reports, as well as single case reports not covered in the review, documented comparable features as well as cuffless encasement of the wire track. Only scattered lymphocytes in the vicinity of the electrode tracks have been reported. In addition to the case reported here, we have examined an autopsy case of a 73-year-old man with Parkinson disease whose tremor was treated with bilateral subthalamic stimulators for four years. The minor histological changes were similar to those previously reported in literature. One post-mortem study used electron microscopy to examine fragments of brain tissue attached to 21 explanted DBS electrodes. The authors speculated that electron-dense inclusions in microglia were fragments of polyurethane.

This case stands out from previously published cases by virtue of the intense lymphocytic infiltrate at the electrode sites. There are several possible explanations for this. First, this might simply reflect an extreme of the body’s response to platinum-iridium electrodes or polyurethane degradation products.
However, our observation that the foreign body giant cells with refractile material were not associated with lysosomes argues against this point. Second, this could represent a response to small quantities of residual dibutyl phthalate in the polyurethane coating of the wire leads, although there is no evidence in the toxicology literature to support such an inflammatory response. Third, the reaction could represent a local exacerbation of foreign body giant cell inflammation in the setting of a systemic viral illness. Such a phenomenon has been suggested in the dental implant literature. Supporting this hypothesis is the fact that the man had evidence of similar focal contamination in the heart. Furthermore, within a few weeks of the reported case, three other autopsy cases with incidental mild focal encephalitis were encountered. A variety of common, usually benign, seasonal enteroviruses are capable of causing myocarditis and encephalitis. To what extent the brain inflammation contributed to the man's death is unknown.

Acknowledgements

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Disclosures

Dr. Del Bigio holds the Canada Research Chair in Developmental Neuropathology.

References


IN MEMORIAM

Ellsworth C. (Buster) Alvord, Jr. (1923-2010)

Dr. Ellsworth C. (Buster) Alvord, Jr., eminence grise of American neuropathology and longstanding member of the American Society of Neuropathologists, died following a series of strokes on July 20, 2010.

The genesis of Dr. Alvord's career in neuropathology occurred while a medical student at Cornell University through the formative guidance of Dr. J. Donald Stevenson. Following his graduation in 1946, Dr. Alvord undertook a postgraduate training program at the New York Hospital-Cornell Medical Center, where he was mentored by Drs. Walter Reed General (1948-1950), neuropathology (Armed Forces Institute of Pathology 1950-1951), and neurology (National Institute of Neurological Diseases and Blindness, where he had been Chief of the Clinical Neurology Section (1955-1959), and with his colleague, Dr. Cheng-Mei Shaw. After moving to the University of Washington in 1960 to become Professor Emeritus of Neurology and chief of the Neurology Service, he devoted his career to teaching, continuing to lecture on the fundamental aspects of neurology and its complications. His major contributions to the understanding of the immunology, development of a model of chronic remitting disease, and devising treatment protocols with monoclonal antibodies. He is known for his research on multiple sclerosis.

The Laboratory at Washington University became a research cornerstone of neurological medical care in the Pacific Northwest and beyond. From this repository came many of the foundations of modern scientific research and clinical care. Today, Dr. Alvord's laboratory at the University of Washington is a major player in the research of neurodegenerative diseases, with a focus on multiple sclerosis.

Edward Stilvorth Johnson, Edmonston, Alberta

Dr. Alvord's contributions to the field of neurourology have been widely recognized, and his legacy will continue to influence the field of neurourology for many years to come.

A dedicated tribute to Dr. Alvord is forthcoming in the Journal of Neurology, Neurosurgery, and Psychiatry.