Published in final edited form as:

Parkinsonism Relat Disord. 2018 September ; 54: 51–55. doi:10.1016/j.parkreldis.2018.04.009.

Deep Brain Stimulation Associated Gliosis: A Post-mortem Study

Vinata Vedam-Mai, Ph.D.^{1,2,*,#}, Cooper Rodgers, BS¹, Ashley Gureck, BS¹, Michael Vincent, BS¹, Gianna Ippolito¹, Ahmad Elkouzi², Anthony T. Yachnis, M.D.³, Kelly D. Foote, M.D.¹, and Michael S. Okun, M.D.^{2,#}

¹Department of Neurosurgery, McKnight Brain Institute, University of FL, Gainesville, FL 32610-0015

²Department of Neurology, UF Center for Movement Disorders and Restoration, Gainesville, FL

³Department of Pathology and Immunology, University of FL, Gainesville FL 32610-0015

Abstract

Background—DBS is a well-established therapy for patients with PD and is an emerging therapy for other neuropsychiatric disorders. Despite the rise in DBS usage, relatively little is known about the tissue and cellular responses to DBS.

Purpose—To examine post-mortem effects of DBS leads by objectively quantifying gliosis around the distal DBS lead tip.

Methods—The UF DBS Brain Bank repository currently has 64 brains, of which 18 cases met criteria for this study.

Results—The average patient age was 54.88 ± 13.43 years (mean $\pm$ SD), male:female ratio was 3:1, average disease duration was 20.70 ± 6.36 years and average DBS duration was 7.26 ± 6.36 years. Microscopic evaluation revealed tissue reaction and astrocytic responses to the lead. Significant fibrosis was seen in n=2 brains and prominent microglial response in n=1. Mean gliotic collar measured from H&E and GFAP staining was 122.5 microns and 162.5 microns,

*Corresponding author info: Dr. Vinata Vedam-Mai, McKnight Brain Institute, L3-171, Dept. of Neurosurgery, University of Florida, Gainesville 32611. vinved@neurosurgery.ufl.edu, (352) 273-8583.

#VVM and MSO share senior authorship

Author Roles:

VVM designed, performed and supervised experiments conducted at University of Florida. VVM collated the data, prepared the figures and composed the manuscript. CR, AG, MV, GI performed statistical analysis, designed the tables and figures and composed parts of the manuscript. ATY provided neuropathological diagnosis and gliosis measurements. AE and KDF provided scientific advice and MSO provided the conception of the paper, critical revisions, and overall supervision for this project.

Financial Disclosure/CoI: There are no conflicts of interest or financial disclosures for CR, AG, MV, GI, AE, ATY, KDF. VVM and MSO report grant from St. Jude/Abbott. Funding Source: Abbott/St. Jude Medical.

Financial Disclosures:

VVM has funding from Abbott/St. Jude Medical. MSO reports grants from NIH, Medtronic, Abbvie, Abbott/St. Jude, MJFF, Bachmann-Strauss, outside of the submitted work. KDF has had funding from NIH, Medtronic, Abbott/St. Jude, Boston Scientific, Neuropace and Functional Neuromodulation.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

respectively. Mean gliotic thickness at the DBS electrode lead tip was $119.13 \pm 64.29 \mu\text{m}$ for patients receiving DBS for 0–5 years, $127.85 \pm 94.34 \mu\text{m}$ for 5–10 years and $111.73 \pm 114.18 \mu\text{m}$ for patients with DBS >10 years. Kruskal-Wallis one-way analysis of variance (ANOVA) revealed no statistically significant differences between DBS duration and amount of gliosis.

Conclusions—This study revealed that approximately three out of four post-mortem DBS cases exhibited pathological evidence of a glial collar or scar present at the ventral DBS lead tip. The amount of gliosis was not significantly associated with duration of DBS. Future studies should include serial sectioning across all DBS contacts with correlation to the volume of tissue activation and to the clinical outcome.

Keywords

Deep brain stimulation; Parkinson's disease; Neuropathology; Gliosis

Introduction

Despite the increase in DBS use for the treatment of movement and neuropsychiatric disorders, there remains an open question as to the impact of the implantation (microlesion) effect upon surrounding tissue. There have been several recent cases of mild gliosis reported and these cases have been largely attributed to inflammatory changes [2]. The tissue response has been thought to be at least partially due to an activated microglial response to subcortical tissue and also due to capillary damage and disruption of neuronal cell processes [10]. It has been hypothesized that there is a mechanically induced reactive response and this response may be clinically beneficial [4]. Another possibility is that the inflammatory response leads to the development of a glial scar in the region of the implanted probes. There has been a worry in the field that a gliotic scar may form around the center of the active DBS contact this gliosis may possibly disrupt or impede the electrical output [5]. The long-term adverse effects of gliosis and fibrosis on DBS outcomes remain unknown.

Despite the global rise in DBS usage, there exists a paucity of brain tissue repositories available to address topics such as the microlesion effect. The primary objective of this study was to examine (ventral) DBS lead tips to ascertain if there was a consistent tissue response to insertion of the DBS device. We aimed to characterize and quantify post-implantation gliosis and to examine any potential effect over time.

Methods

Patient Protocol, Tissue Acquisition and Storage

Prior to death, informed consent was obtained through a previously approved UF IRB protocol for each subject. DBS brain specimens were collected from a several different geographical locations within the US, including from inside and outside the University of Florida system. DBS brains from previously consented donors were harvested, collected, and processed according to the SOP described in the published DBS-BTN pilot study [11]. Complete data files were created and recorded for each donor. The data assessed for the current study included diagnosis, duration of disease, DBS duration, age of death, sex, and perceived effectiveness of the DBS.

The brains were dissected and the regions that would be utilized for tissue processing were selected and standard tissue processing was employed as previously described in the Columbia Brain Bank Protocol [12]. Our protocol allowed retention and storage of the remaining portions of the brain in a phosphate-buffered saline (PBS) solution. Brains were placed in a vacuum-sealed bag for any additional histopathological examination.

Fixation and Blocking, Histopathological Methods, Immunohistochemistry

While harvesting the brains, the DBS leads were kept intact and fixed with 10% Zn-buffered formalin fixative solution for approximately 1–2 weeks prior to dissection. The brain was sectioned in the coronal plane into 3-cm slabs to obtain adequate brain tissue surrounding the DBS lead. The brain was subsequently sectioned in 1-cm intervals. Representative tissue samples were obtained and the remaining portion of the brain was stored. Tissue samples were then paraffin embedded, sectioned, and stained with the standard hematoxylin-eosin (H&E) tissue staining method.

To aid in the evaluation of any associated astrocytic gliosis present at the distal (ventral) lead tip, an immunohistochemical study was performed for glial fibrillary acidic protein (GFAP). GFAP is an intermediate filament protein that is found in glial cells and is primarily up-regulated by reactive astrocytes as a result of CNS trauma or neurodegenerative conditions [9]. Additionally, Masson's Trichrome staining was performed in order to evaluate collagen accumulation in the region of the lead tip. Other immunohistochemical studies that were performed consisted of antibodies for α -synuclein, β -amyloid peptide, and hyperphosphorylated τ .

Standard immunohistochemistry was performed on the representative tissue sections to confirm pathological diagnosis. Disease diagnosis was established based on histopathological findings by a Board-Certified Neuropathologist and diagnosis was based on published criteria [1; 13; 6].

Gliotic Measurements and Statistical Analysis

The thickness of the dense part of the glial scar was measured on the sections at the lead tip defect stained with H&E. An anti-GFAP antibody was used for staining. For each section, five different measurements were taken using the Olympus DX41 microscope and Olympus cellSens Imaging Software. The results have been presented as an average thickness per section/zone. Samples were categorized into three groups based on DBS duration: 0–5y, 5–10y and >10y. Bilateral cases were treated as individual samples. In order to meet the requirements for measurement, the case was confirmed to have a complete data file, an H&E stained slide, and a GFAP stained slide of the DBS distal lead tip defect. The GraphPad™ Prism 7 Software was used to run a one-way ANOVA analysis and Mann-Whitney statistical test.

Results

Demographic, Disease, and DBS Information

Of the 64 total brains, 18 cases met the inclusion criteria for the study (n=18). The average patient age at disease onset was 54.88 ± 13.43 years with a male:female ratio of 3:1. The average disease duration was 20.70 ± 6.36 years and the average DBS duration was 7.26 ± 6.36 years. PD was the diagnosis in 14 cases (77.7%), MSA was the diagnosis in 1 case (5.5%). 1 case had a clinical presentation of Parkinsonism, with a levodopa response, with refractory tremor as an indication for DBS. Pathology revealed extensive A-beta amyloid-immunoreactive neuritic and diffuse plaques, with minimal τ pathology and no α -synuclein pathology. Parkinsonism with AD-like changes upon pathology was the diagnosis in 1 case (5.5%) and ET was the diagnosis in 2 cases (11.11%). The most commonly targeted region with a DBS lead was the subthalamic nucleus with STN=23, followed by globus pallidus interna with GPi=4, Ventralis Intermedius (VIM)=1, and Paramedian Pontine Nucleus (PPN)=2.

Extent of Gliotic Response around DBS Lead Tip Defect

The thickness of the gliotic collar was measured using standard H&E (Figure 2.1–2.3) staining as well as GFAP (Figure 2.4–2.6) staining. Twenty-five measurements were made with H&E and a total of 8 measurements were made with GFAP. The mean gliotic collar as measured from H&E and GFAP staining was 122.5 microns and 162.5 microns, respectively.

For statistical analysis using H&E measurements, the cases were categorized as follows: Group 0–5 years (n=6 measurements, mean gliotic thickness= $119.13 \pm 64.29 \mu\text{m}$), Group 5–10 years (n=14 measurements, mean gliotic thickness= $127.85 \pm 94.34 \mu\text{m}$), and Group 10 or more years (n=5 measurements, mean gliotic thickness= $111.73 \pm 114.18 \mu\text{m}$) (Figure 1). A one-way ANOVA revealed that DBS duration did not have a statistically significant effect on gliotic scar thickness (Table 2/Figure 1; $P=0.7399$). However, the observed tissue response was less in the patient group with DBS for over 10 years compared with the groups who were stimulated for a lesser duration, i.e. after 0–5 and 5–10 years post implantation. There was no observable trend between DBS duration and the thickness or severity of the gliotic collar (Figure 1).

H&E and GFAP stained sections showed prominent but varying thicknesses of astrocytic scarring around the lead tip defect as shown in Fig. 2.1–2.3 and 2.4–2.6. In some cases, GFAP staining revealed a mix of gliotic and fibrotic responses (Fig 2.6), as seen by the collagenous accumulation close to the electrode tip as well as the presence of an outer ring of reactive astrocytes.

Microscopic observations also revealed the presence of focal hemosiderin deposits in addition to gliosis as well as Rosenthal-like fibers (Fig. 2.3). Hemosiderin deposition was suggestive of hemorrhage most likely associated with the electrode implantation. Rosenthal fibers were characteristic of long-standing gliosis and were readily identifiable as thick, elongated, corkscrew-shaped eosinophilic bundles.

Gliotic Response at active contact

In order to assess whether there were any differences in gliosis when the tissue was obtained from around a ventral active contact vs dorsal active contact, we compiled all information available on active DBS contacts from our dataset. 0 and 1- were designated as ventral cathodes and 2-, 3- were designated dorsal cathodes. A comparison was made of the thickness of gliotic response when the active contact was dorsal to when the active contact was ventral. Table 3 summarizes lead contact with respect to gliotic thickness. When gliotic responses of ventral vs. dorsal active lead were compared, there was a slight trend in increase of gliosis when the active contact was ventral, however it did not reach statistical significance ($P=0.54$, Mann-Whitney non-parametric test) (Fig. 3).

Discussion

This study revealed that approximately three out of four post-mortem DBS cases exhibited pathological evidence of a glial collar or scar at the ventral DBS lead tip. Disease duration did not correlate with severity of the scar (Table 2, Figure 1). Our findings were similar to the results observed in other smaller studies of post-mortem human brains, which revealed mild astrogliosis and a thin collagen layer lining the lumen of the electrode tract [3; 7]. The gliotic response surrounding the DBS lead tip has been attributed to the brain's reactivity to the electrode itself, and/or to chronic electrical stimulation [2; 10; 4], though in our case it was likely that there was not active stimulation at the ventral defect. The average measured gliotic collar ranged from 20–360 microns and there were no other neuroinflammatory responses. In the cases that had fibrosis confirmed by Masson's Trichrome staining, there was a collagenous capsule that surrounded the lumen of the lead tip defect with gliosis comprising the outermost border of this capsule [2]. There was an observable asymmetrical gliotic response in some of the cases. In other specimens, asymmetrical gliosis was seen with a greater response on one side of the defect. The level of severity of the gliotic response differed on a case-by-case basis and could not be attributed to the duration of DBS. We observed an initial gliotic response (statistically insignificant), which subsided with time. This observation supported a trend in decreased tissue reactivity and glial response after implantation, though our sample size was too small to confirm the observation [8]. Demonstration of stability in gliosis would presumably support the idea of long term biocompatibility of the DBS device [4] [5].

Future post-mortem studies are ongoing, and are focused on serial sectioning and marking the location of the center of the activated DBS contact. This procedure will be critical to separate lesion and stimulation induced effects. Further, future studies should include a detailed comparison of any differences in gliosis between tissue obtained from ventrally stimulated and dorsally stimulated contacts as well as details on the effects on white matter. Studies should assess for potential correlation between gliotic scarring and the clinical efficacy of DBS therapy. In summary, there was frequently a mild gliosis present around the ventral DBS lead tip. This pathological response may possibly contribute to the microlesion effect.

Acknowledgments

We would like to acknowledge the support of the University of Florida Parkinson's Foundation Center of Excellence, the UF DBS Brain Tissue Network, the Abbott Brain Tissue Bank, and the UF Foundation.

References

- Braak E, Sandmann-Keil D, Rub U, Gai WP, de Vos RA, Steur EN, Arai K, Braak H. alpha-synuclein immunopositive Parkinson's disease-related inclusion bodies in lower brain stem nuclei. *Acta Neuropathol.* 2001; 101:195–201. [PubMed: 11307617]
- Haberler C, Alesch F, Mazal PR, Pilz P, Jellinger K, Pinter MM, Hainfellner JA, Budka H. No tissue damage by chronic deep brain stimulation in Parkinson's disease. *Ann Neurol.* 2000; 48:372–376. [PubMed: 10976644]
- Henderson JM, Pell M, O'Sullivan DJ, McCusker EA, Fung VS, Hedges P, Halliday GM. Postmortem analysis of bilateral subthalamic electrode implants in Parkinson's disease. *Mov Disord.* 2002; 17:133–137. [PubMed: 11835450]
- Marin C, Fernández E. Biocompatibility of Intracortical Microelectrodes: Current Status and Future Prospects. *Frontiers in Neuroengineering.* 2010; 3:8. [PubMed: 20577634]
- McConnell GC, Rees HD, Levey AI, Gutekunst CA, Gross RE, Bellamkonda RV. Implanted neural electrodes cause chronic, local inflammation that is correlated with local neurodegeneration. *J Neural Eng.* 2009; 6:056003. [PubMed: 19700815]
- McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Lodos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology.* 2005; 65:1863–1872. [PubMed: 16237129]
- Nielsen MS, Bjarkam CR, Sorensen JC, Bojsen-Moller M, Sunde NA, Ostergaard K. Chronic subthalamic high-frequency deep brain stimulation in Parkinson's disease--a histopathological study. *Eur J Neurol.* 2007; 14:132–138. [PubMed: 17250719]
- Orlowski D, Michalis A, Glud AN, Korshoj AR, Fitting LM, Mikkelsen TW, Mercanzini A, Jordan A, Dransart A, Sorensen JC. Brain Tissue Reaction to Deep Brain Stimulation-A Longitudinal Study of DBS in the Goettingen Minipig. *Neuromodulation.* 2017
- Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. *Glia.* 2005; 50:427–434. [PubMed: 15846805]
- Polikov VS, Tresco PA, Reichert WM. Response of brain tissue to chronically implanted neural electrodes. *J Neurosci Methods.* 2005; 148:1–18. [PubMed: 16198003]
- Vedam-Mai V, Krock N, Ullman M, Foote KD, Shain W, Smith K, Yachnis AT, Steindler D, Reynolds B, Merritt S, Pagan F, Marjama-Lyons J, Hogarth P, Resnick AS, Zeilman P, Okun MS. The national DBS brain tissue network pilot study: need for more tissue and more standardization. *Cell Tissue Bank.* 2011; 12:219–231. [PubMed: 20589432]
- Vonsattel JPG, Amaya MdP, Cortes EP, Mancevska K, Keller CE. 21st Century Brain Banking Practical prerequisites and lessons from the past: The experience of New York Brain Bank – Taub Institute - Columbia University. *Cell Tissue Bank.* 2008; 9:247–258. [PubMed: 18581261]
- Waldvogel HJ, Curtis MA, Baer K, Rees MI, Faull RL. Immunohistochemical staining of post-mortem adult human brain sections. *Nat Protoc.* 2006; 1:2719–2732. [PubMed: 17406528]

- Tissue response to Deep Brain Stimulation (DBS) is studied using neuropathological methods.
- Gliosis is associated with DBS, in the immediate vicinity of the electrode.
- DBS duration is not significantly correlated with extent of gliotic scarring.

Figure 1. Results of Kruskal-Wallis one-way analysis of variance test for comparison of DBS duration and its' effects on gliotic response

There were no significant differences between DBS duration and the effect on the gliotic response of surrounding tissue ($p=0.7339$).

Figure 2. Histological and immunohistochemical representation

H&E (1–3) and GFAP (4–6) staining of cases with differing levels of severity of gliotic response. Level of severity was classified as follows: Mild = < 100 μ m, Moderate = 100–200 μ m, Severe = > 200 μ m. **1.** Left subthalamic nucleus (STN) at 10x magnification displaying a more typical mild gliotic response. **2.** Right STN at 10x, with a moderate amount of gliotic thickness. **3.** Right STN with lead tip defect, with focal hemosiderin deposition with a severe gliotic collar and scattered Rosenthal-like fibers. **4/5.** Both sections demonstrate examples of mild-moderate gliosis in the right STN at 10x magnification. **6.** Left pedunculopontine nucleus (PPN) at 10x displaying very prominent focal fibrosis along with a surrounding severe gliotic response.

Figure 3. Results of Mann-Whitney nonparametric test for comparison of active lead contact and its effect on gliotic response

There was no significant difference between gliosis of surrounding tissue response as a function of active contact (ventral/dorsal) ($P=0.54$).

Table 1

Demographic Information

Chart of Demographic information from cases with complete data files (54) compiled by pathological disease diagnosis.

Disease	N	Sex (Male: Female)	Average Age of Onset (years)	Average DBS Duration (years)	Average Duration of Disease (years)
Parkinson's Disease	14	12:2	52.92	7.19	21.84
Multiple System Atrophy	1	0:1	50	7	9
Essential Tremor	2	1:1	58	8.5	20.5
Other	1*	1:0	79	6	7
Total	18	14:4	46.8	4.92	21.35

* Clinical presentation of Parkinsonism, with a levodopa response. Indication for DBS was refractory tremor. Pathology revealed extensive A-beta amyloid-immunoreactive neuritic and diffuse plaques with minimal tau pathology and no alpha-synuclein pathology.

Table 2
Effect of DBS duration on gliosis

Results of Kruskal-Wallis one-way ANOVA test examining the effect of DBS duration on gliotic response. There were no significant differences in gliotic thickness between the DBS duration groups (P=0.7339)

DBS Duration (years)	N	Gliotic Thickness in Microns (Mean $\pm$ SD)	P-Value ^a
0–5	6	119.13 $\pm$ 64.29	P= 0.7399
5–10	14	127.85 $\pm$ 94.34	
>10	5	111.73 $\pm$ 114.18	

^a the P-value was assessed using a Kruskal-Wallis one-way ANOVA.

Table 3
Gliososis response with respect to DBS lead contact position

Compilation of gliotic response with respect to active lead contact. Mann-Whitney test examining the effect of DBS active contact on gliotic response revealed that there were no significant differences in gliotic thickness between the ventral and dorsal groups ($P=0.54$).

Ventral (gliosis in um)	Dorsal (gliosis in um)
104.966	66.674
53.238	100.076
68.01	131.694
20.344	77.886
274.46	70.406
98.64	47.014
76.81	222.814
137.308	117.33
98.64	37.2
310.88	89
111.046	
Avg. thickness um 123.122	96.0094