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Deep Brain Stimulation Response in Pathologically Confirmed Cases of Multiple System Atrophy

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Abstract

Deep brain stimulation is a treatment for select cases of medication refractory movement disorders including Parkinson's disease. Deep brain stimulation has not been recommended for treatment in multiple system atrophy patients. However, the paucity of literature documenting the effects of deep brain stimulation in multiple system atrophy patients and the revelation of a levodopa-responsive subtype of multiple system atrophy suggests further investigation is necessary.

This study summarizes the positive and negative effects of deep brain stimulation treatment in two pathologically confirmed multiple system atrophy patients from the University of Florida Deep Brain Stimulation-Brain Tissue Network. Clinical diagnosis for the two patient cases did not match the neuropathological diagnosis. We noted that in both pathologically confirmed multiple system atrophy patients, death occurred as a result of myocardial infarction. Importantly, there was reported transient benefit in levodopa responsive features that indicate deep brain stimulation may be an option for select multiple system atrophy patients.

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Keywords

Deep Brain Stimulation; Pathology; Multiple System Atrophy

Introduction

Parkinson's disease (PD) is a neurodegenerative syndrome most often classified by its clinical features including tremor, rigidity, bradykinesia, postural instability, asymmetric onset, and levodopa responsiveness [1,2]. Non-motor features of PD are also often present and may include depression, anxiety, apathy, sexual dysfunction, cognitive dysfunction as well as the possibility of autonomic manifestations [1]. Multiple system atrophy (MSA) often presents with symptoms similar to Parkinson's disease (PD), and is the most common neurodegenerative syndrome confused with PD when selecting candidates for deep brain stimulation (DBS) surgery [3]. Patients with MSA typically fail to, or only minimally, improve with levodopa treatment, present with autonomic dysfunction, have less asymmetric features, and are characterized by a more progressive disease course when compared to PD [1,2].

The unique pathological feature of MSA is the formation of alpha-synuclein-reactive glial cytoplasmic inclusions mainly in oligodendroglia. These inclusions are distinct from the Lewy bodies found in PD which can be most commonly observed in dopaminergic neurons. MSA clinically manifests itself differently than PD with subtypes including severe parkinsonism (striatonigral degeneration, MSA-P), severe autonomic dysfunction (Shy-Drager syndrome, MSA-A), and cerebellar dysfunction (olivopontocerebellar degeneration, MSA-C) [1]. It is thought that the pathologies of these various subtypes are identical, or at least similar; the cause of phenotypic differences remains unclear. There has been a recent, growing appreciation for MSA cases that appear to be clinically similar to PD and respond to levodopa during the first five or more years following diagnosis [4–7]. The similarity of clinical symptoms and the lack of a definitive clinical diagnostic test have contributed to DBS implantation in presumed PD cases, which are later diagnosed with MSA [1,7].

The effectiveness of DBS in treating PD has been well established, however, there are very few cases of pathologically confirmed MSA patients that have undergone DBS. Furthermore, it has been the general consensus among neurological practitioners that DBS in MSA patients is largely ineffective [3–5,8]. However, because levodopa responsiveness has been directly correlated to DBS efficacy in PD, addressing DBS effects on specific levodopa responsive symptoms in MSA may be worth considering [5,6].

We hypothesized that levodopa-responsive MSA patients may benefit from DBS therapy. In this study we reviewed the records of pathologically confirmed cases of MSA from the University of Florida (UF) Deep Brain Stimulation-Brain Tissue Network (DBS-BTN).

Methods

A retrospective chart review of the UF Institutional Review Board approved DBS-BTN was performed to identify DBS patients with a pathological diagnosis of MSA. The DBS-BTN includes de-identified post-mortem DBS cases from 11 different institutions from all over the United States of America. Clinical histories were reviewed for signs of MSA (early and/or severe autonomic symptoms, early erectile dysfunction, poor levodopa response, respiratory stridor, and any cerebellar features). These features were derived from the current consensus criteria for MSA diagnosis [9]. Additionally, all pre-operative, post-operative, Unified Parkinson's Disease Rating Scale (UPDRS) were recorded. Patient and

clinician perceived outcomes were reviewed to assess the clinical response to DBS among these patients.

Results

Twenty-two cases from the DBS-BTN were reviewed (n=22). Two patients were clinically diagnosed with PD, but found to have MSA on neuropathology.

Patient one

A 60-year-old Hispanic man was diagnosed with PD in 1998 after noticing a resting tremor in his right upper extremity that gradually spread to his left upper extremity. His past medical history included a knee surgery in 1960, a left hip replacement, and a left ankle repair in 1983 (the latter two were the result of a motor vehicle accident). He reported that when his medication (carbidopa/levodopa 25/100 mg 2 tablets 6 times daily plus 1 tablet at bedtime) was effective, he felt “on” and nearly normal. In the “off” medication state, he reported severe disability. He had approximately 7.2 to 8.4 hours in the “off” state per day. The patient experienced peak dose dyskinesias approximately 35% of the time and experienced dysphagia with occasional choking. The patient also used sildenafil citrate (Viagra®) for erectile dysfunction.

In February 2004, he underwent a DBS implantation on the left side in the globus pallidus internus (GPi) for progressive PD with prominent symptoms of bradykinesia, rigidity, painful dystonias, hypophonic speech, and gait instability. The procedure was performed to improve the patient’s parkinsonian symptoms and to increase “on time.” The measured lead tip location for the left lead was $-24.6, -0.5, -3.6$ (x,y,z), and was felt to be lateral to the optimal position. Following surgery, he developed expressive aphasia (that resolved over several weeks with therapy) and he later developed a worsening gait. Brain MRI revealed a lacunar infarct in the pallidum/internal capsule region. The left GPi-DBS and stroke reportedly improved his right hemibody parkinsonian symptoms. Although the DBS lead was sub-optimally placed, the infarct may have offered a beneficial lesion effect. Contralateral DBS was performed to alleviate left-sided parkinsonian symptoms. In February 2005, the patient underwent right GPi-DBS implantation and repositioning of his left DBS lead. The measured lead tip location for the right lead was $22.19, 4.79, -2.5$ (x,y,z), and the measured lead tip location for the revised left lead was $-20.69, 7.2, 11.5$ (x,y,z). The left lead was dorsally placed anterior and shallow to the optimal location, but he reported satisfactory improvement in his symptoms. Axial and gait symptoms remained unresponsive to medications and to DBS. Complications after the second DBS procedure included worsening of his speech intelligibility and pronounced sialorrhea. It was unclear from the DBS-BTN notes whether this was a direct result of surgery, or due to natural disease progression. His UPDRS scores pre- and post-operatively are summarized in Table 1. Only the UPDRS total scores, not the sub-parameters, were available for review. Consequently an evaluation of the difference in the beneficial effects of levodopa and DBS could not be made.

The patient expired at the age of 70 from a myocardial infarction. His pathological examination revealed diffuse, bilateral putaminal degeneration characterized by atrophy, and pronounced chronic astrogliosis suggestive of striatonigral degeneration. Oligodendroglial inclusion bodies were noted. Two organized and centrally cavitated old lacunar infarcts, one in the mid left pallidum, and one (or possibly two) in the posterior pallidum and/or internal capsular posterior limb were also noted. Pathological findings were consistent with MSA

Patient two

A 54-year-old Caucasian man developed a left hand tremor in 2004 and was diagnosed with idiopathic PD. His past medical history included multiple coronary stents and previous implantation of a urinary stimulator. He was initially treated with ropinirole and reported initial benefit, but he gradually required an increase in dosage to 21 mg per day. Carbidopa/levodopa was added after he no longer obtained benefit from the ropinirole. He experienced dyskinesias in both lower extremities and in the face. The patient also had difficulty with sleeping, constipation, dyspnea, orthopnea, frequent urination, and sexual dysfunction.

He initially responded to carbidopa/levodopa, but he developed resistance in his gait and balance problems. In April 2007, a unilateral STN-DBS implantation was performed to alleviate motor fluctuations, dyskinesias, and tremors. He had clinician perceived dramatic improvement in his facial expressivity, volume of speech, and speed of gait and turn. However, in April 2008, both the patient and his clinician described his overall state compared to before DBS surgery as “minimally improved.” The patient was concerned that he was deriving less benefit over time from unilateral DBS and requested contralateral DBS in hopes of achieving similar benefit to that observed from the initial right-side DBS. In November 2008, a left STN-DBS lead was implanted. The measured ventral lead tip location for the right lead was 12.03, -3.08, -4.5 (x,y,z) and the measured ventral lead tip location for the left lead was -11.33, -2.2, -7.08 (x,y,z). Unfortunately, the patient expired shortly after implantation of the internal pulse generator from a myocardial infarction (approximately five years after initial diagnosis and 40 months after initial DBS implantation). The second DBS device was never activated. Neuropathological examination revealed extensive α -synuclein-reactive glial cytoplasmic inclusions consistent with a pathological diagnosis of MSA.

Discussion

The data presented in this report from the UF DBS-BTN shows transient benefit from DBS in MSA patients. In both patients, the improvements perceived by the patient and the clinician, as well as UPDRS Part III scores, support a transient benefit from DBS implantation in pathologically confirmed MSA patients (Table 1). Though there may be only a transient benefit from DBS in levodopa responsive MSA features, some may argue that DBS is a viable treatment option to improve quality of life for very select MSA-P patients especially since the lifespan after onset of symptoms is only between 6.1 years and 9.5 years, and symptomatic therapy for MSA-P is limited [10]. It is important to note that both patients did show initial benefit from levodopa treatment that declined over time and required a gradual increase in dosage.

Our study emphasizes the difficulty involved when making a clinical diagnosis of PD versus MSA as well as the critical need for improved diagnostic modalities. Inaccurate clinical diagnoses have been shown to account for a significant portion of reported DBS “failures” and highlight the importance of pathological confirmation to ensure that studies of DBS efficacy are not biased by the inaccuracy of clinical diagnosis [11].

The literature contains several cases where death occurred shortly after DBS implantation in MSA patients, as occurred with patient two [3,4]. Post-mortem examination showed that both pathologically confirmed MSA patients expired from myocardial infarctions. Patient one showed no early cardiac problems, but pathologic evaluation revealed arterial/arteriolar sclerosis. Patient two had atherosclerotic coronary artery disease, but no reported dysautonomia. There is one case report in the literature of transient left ventricular apical ballooning at the onset of MSA associated with cardiomyopathy [12]. Interestingly, of the 22 DBS-BTN patients, only four patients had cardiac related causes of death; two of whom

had MSA. Only 10% of the PD patients expired from a cardiac related cause. The statistical significance of the myocardial infarctions as a cause of death in the MSA patients cannot be determined given the small sample size of pathologically confirmed MSA patients (n=2), but the data from this case series suggest that myocardial infarction as a cause of death in post-DBS MSA cases may need closer investigation.

This case series would have been enhanced by a complete clinical dataset and a larger sample size. Additionally, because both pathologically confirmed MSA patients had late-stage MSA with few remaining neurons and little neuronal cytoplasmic inclusions, the correlation between specific autopsy neuropathology and specific clinical/therapeutic parameters was poor. Although limited, the observations of the current case series remain valuable as they point toward the possibility that MSA patients may marginally benefit from DBS.

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References

1. Bhidayasiri R, Ling H. Multiple system atrophy. *Neurologist*. 2008 Jul; 14(4):224–237. [PubMed: 18617848]
2. Kollensperger M, Geser F, Seppi K, Stampfer-Kountchev M, Sawires M, Scherfler C, et al. Red flags for multiple system atrophy. *Mov Disord*. 2008 Jun 15; 23(8):1093–1099. [PubMed: 18442131]
3. Shih LC, Tarsy D. Deep brain stimulation for the treatment of atypical parkinsonism. *Movement Disorders*. 2007; 22(15):2149–2155. [PubMed: 17659638]
4. Tarsy D, Apetauerova D, Ryan P, Norregaard T. Adverse effects of subthalamic nucleus DBS in a patient with multiple system atrophy. 2003; 61(2):3.
5. Chou KL, Forman MS, Trojanowski JQ, Hurtig HI, Baltuch GH. Subthalamic nucleus deep brain stimulation in a patient with levodopa-responsive multiple system atrophy. Case report. *J Neurosurg*. 2004 Mar; 100(3):553–556. [PubMed: 15035294]
6. Wenning GK, Tison F, Ben Shlomo Y, Daniel SE, Quinn NP. Multiple system atrophy: a review of 203 pathologically proven cases. *Mov Disord*. 1997 Mar; 12(2):133–147. [PubMed: 9087971]
7. Lezcano E, Gomez-Esteban JC, Zarranz JJ, Alcaraz R, Atares B, Bilbao G, et al. Parkinson's disease-like presentation of multiple system atrophy with poor response to STN stimulation: a clinicopathological case report. *Mov Disord*. 2004 Aug; 19(8):973–977. [PubMed: 15300669]
8. Santens P, Vonck K, De Letter M, Van Driessche K, Sieben A, De Reuck J, et al. Deep brain stimulation of the internal pallidum in multiple system atrophy. *Parkinsonism Relat Disord*. 2006 Apr; 12(3):181–183. [PubMed: 16338160]
9. Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*. 2008 Aug 26; 71(9):670–676. [PubMed: 18725592]
10. Visser-Vandewalle V, Temel Y, Colle H, van der Linden C. Bilateral high-frequency stimulation of the subthalamic nucleus in patients with multiple system atrophy--parkinsonism. Report of four cases. *J Neurosurg*. 2003 Apr; 98(4):882–887. [PubMed: 12691416]
11. Okun MS, Tagliati M, Pourfar M, Fernandez HH, Rodriguez RL, Alterman RL, et al. Management of referred deep brain stimulation failures: a retrospective analysis from 2 movement disorders centers. *Arch Neurol*. 2005 Aug; 62(8):1250–1255. [PubMed: 15956104]
12. Ripa S, Scaglione C, Rusconi LC. Transient left ventricular apical ballooning at the onset of multiple system atrophy. *J Cardiovasc Med*. 2006; 7(8):631–636.10.2459/01.JCM.0000237913.12915.13

Table 1

Patient Characteristics

	Age	Disease Duration (years)	Clinical Diagnosis	Pathologically-Confirmed Diagnosis	Cause of Death
Patient one	70	9	PD	MSA	Myocardial Infarction
Patient two	59	5	PD	MSA	Myocardial infarction

Table 2

UPDRS III Preoperative and Postoperative Scores

Total UPDRS Scores	Preoperative		Unilateral DBS		Bilateral DBS	
	Off Med	On Med	Off Med	On Med	Off Med	On Med
Patient one *	52	26	34	29	39	36
Patient two **	43	27	N/A	N/A	N/A	N/A

DBS – Deep Brain Stimulation

Med - Medication

UPDRS – Unified Parkinson’s Disease Rating Scale Part III

N/A – Not Available

* Patient one’s UPDRS’s were affected by a prior fracture in the left hand in such a way that the bradykinesia tasks could not be performed

** Patient two had initial DBS surgery at outside institution. Limited UPDRS data was available for this case study.