Pedunculopontine Nucleus Deep Brain Stimulation produces sustained improvement in Primary Progressive Freezing of Gait.

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ABSTRACT

Objective: To assess the efficacy of bilateral pedunculopontine nucleus deep brain stimulation (PPN-DBS) as a treatment for primary progressive freezing of gait (PPFG).

Methods: Our patient with PPFG underwent bilateral pedunculopontine nucleus deep brain stimulation surgery (PPN-DBS) and was followed clinically for over 14 months.

Results: The PPFG patient exhibited a robust improvement in gait and posture following PPN-DBS. When PPN stimulation was deactivated postural stability and gait skills declined to pre-DBS levels and FDG-PET revealed hypoactive cerebellar and brainstem regions, which significantly normalised when PPN stimulation was reactivated.

Conclusions: This case demonstrates that the advantages of PPN-DBS may not be limited to addressing freezing of gait (FOG) in idiopathic Parkinson's disease. The PPN may also be an effective DBS target to address other forms of central gait failure.

INTRODUCTION

Primary progressive freezing of gait (PPFG) is a neurodegenerative disorder that causes gait freezing, postural instability and eventually gait akinesia. It can be associated with Parkinsonian features, particularly bradykinesia, but is generally unresponsive to dopaminergic medications[1]. Freezing of gait (FOG) is the key feature, which is defined as a sudden and transient motor block in walking motion[2]. While FOG occurs in late idiopathic Parkinson's disease (PD) it occurs commonly and early in the atypical Parkinsonian syndromes including progressive supranuclear palsy (PSP), multiple system atrophy, corticobasalganglionic degeneration, vascular Parkinsonism and post-encephalitic Parkinsonism[1]. But it can present in association with normal pressure hydrocephalus and orthostatic tremor[1 3].

The pedunculopontine nucleus (PPN) is a 5mm long, approximately sausage-shaped structure lying in the reticular zone at the junction of midbrain and pons[4]. The PPN appear to play an important role in controlling axial muscle groups that mediate postural stability and gait[5]. PPN-DBS of PD patients with FOG may improve gait[5 6] though success can be variable and non-sustained[7]. We hypothesised that since the PPN has a central role in postural stability and gait that its electrical stimulation might improve gait in a PPFG patient.

METHODS

This 69-year-old male patient presented with an 8-year history of PPFG. In the 12 months pre-operatively his FOG and postural stability worsened, he fell frequently and became increasingly chair and bed-bound. Pre-operative FOG questionnaire (FOG-Q) and gait and falls questionnaire (GF-Q) scores were 16/24 and 39/64 respectively[8].

Cranial MRI revealed mild generalised atrophy, slightly more prominent in the posterior fossa. He was cognitively intact and exhibited mildly reduced arm swing during gait, though no other signs of parkinsonism or PSP[9]. Clinical examination throughout the course revealed normal eye movements, speech and dexterity. However, his gait was broad-based with prominent FOG and postural instability leading to 2 to 3 falls weekly. His gait freezing, posture deficits and falls were unresponsive to L-dopa dose equivalents exceeding 1400 mg/day.

DBS was performed as previously described[10]. CT and 3 tesla MRI FLAIR 1.0mm contiguous axial slices were volumetrically fused (Stealth, Medtronic, Minneapolis, USA) and the PPN targeted on the MRI in stereotactic space. The PPN was located lateral to the superior cerebellar decussation at the level of the inferior colliculus comparing MRI images with brainstem atlases[11]. A trajectory was chosen to approach the nucleus parallel to the axis of the brain stem and 4th ventricle and passing through the subthalamic region posterior to the red nuclei. All electrodes were targeted to lie within the long axis of PPN with the lowest electrode in its rostral aspect. After fixation of the electrodes bilateral Soletra^{TM} (Medtronic) implantable pulse generators (IPG) were placed under anaesthesia[10]. Lead position was confirmed post-operatively via 1.5T MRI.

Bilateral monopolar stimulation of the IPGs was commenced 24 hours post-surgery through the most rostral electrode contact as these were lying within the PPN on postoperative imaging. Initial IPG

parameters were based on those used by Stefani et al. for "on" freezing PD patients with PPN-DBS[12] with rates of 25-30Hz and pulse widths of 60 μs. Slightly higher stimulation rates of 35Hz were optimal in this patient and during the study were; right-IPG 3.5-3.8 Volts, 60μs and 35Hz and left-IPG 2.8-3.3Volts, 60μs and 35Hz. If PPN stimulation was withdrawn, gait function deteriorated to essentially his pre-operative state within 2 minutes (Table 1). Fortunately, gait was restored within 2 minutes of re-activating PPN-IPG stimulation.

INSERT TABLE 1 ABOUT HERE

The patient found inactivation of his PPN stimulators very unpleasant and reporting feelings of unsteadiness and physical exhaustion. Consequently, testing was conducted with frequent rest periods due to the patient's significant risk of falls and injury in the IPGs-off state.

Clinical assessments of gait were regularly performed pre-operatively and post-operatively in various on- and off-states while optimizing IPG parameters. The GF-Q and FOG-Q[8], were used for pre- and post-operative comparison (0, 10, 20, 28, 40 and 60 weeks).

Formal gait assessment and balance was undertaken 4 months pre- and 10 weeks post-operatively. The patient walked at a self-selected pace along a firm walkway with the PPN-DBS stimulators on or off for six trials each. Twenty-eight reflective markers were attached to the body in accordance with the Helen Hayes marker set[13], which was modified to include the trunk and upper extremities. The three-dimensional position of these markers was tracked (200Hz) using a six-camera motion analysis system (Vicon, Oxford, UK), which allowed calculation of temporospatial gait characteristics and the whole-body centre of mass (COM).

Standing balance was assessed post-operatively with PPN-IPGs on and off. The patient stood on a force platform (AMTI, USA) as still as possible for 30 seconds with his eyes open (3 trials) and closed (3 trials). Centre of pressure (COP) data were collected (1000Hz) and provided information on anteroposterior (AP) and mediolateral (ML) postural sway.

F-18FDG-PET studies were performed 22 weeks after DBS surgery. Two segmented Fluorine18 deoxyglucose (F-18FDG) studies were performed 4 days apart with PPN-IPGs turned on and off. These were performed after intravenous administration of 300MBq of F-18FDG using a dedicated Philips Allegro PET scanner (Netherlands). For the off study, the IPGs were turned off for 30 minutes prior to the administration of F-18FDG. The images were reviewed using visual analysis and displayed in a Rainbow colour format with lower threshold of 0 and higher threshold of 8.

RESULTS

GF-Q and FOG-Q scores were recorded the day before DBS surgery and again with IPGs turned on and off at several occasions post-operatively. Clinically the patient exhibited and reported significant improvement in gait stability, reduced episodes of FOG and reduced falls. These observations were mirrored in the improved FOG-Q and GF-Q scores when PPN stimulation was on (Table 1).

PPN-DBS produced significant improvements in most gait parameters, with the exception of step width (Table 2). The patient significantly increased stride length, cadence and walking velocity and reduced time spent in double-limb support. Bilateral PPN-DBS also produced a significant improvement in mediolateral, but not anteroposterior standing balance (Table 2). This was consistent with the patient's report that PPN-DBS had not improved pro- and retropulsion while walking.

INSERT TABLE 2 ABOUT HERE

F-18FDG-PET studies with both PPN-IPG stimulators off were abnormal with a pattern of diffusely decreased FDG uptake compared to normal brain, which was most prominent in the brainstem and both cerebellar hemispheres. With both PPN-IPGs turned on, there was a significant restoration of normal FDG uptake pattern in the brainstem, cerebellar and the cerebral hemispheres (Figure 1). This suggests that electrical stimulation of the PPN acts to return the abnormal FDG uptake pattern towards normal, particularly in the brainstem and cerebellum. This may explain the improved gait parameters, mediolateral postural sway and reduced falls.

INSERT FIGURE 1 ABOUT HERE

DISCUSSION

Several case studies have demonstrated that DBS stimulation of the PPN can improve gait in PD patients with L-dopa resistant FOG[5]. We reasoned that the proposed biological role for the PPN as a controlling element in axial posture and gait, might lead to gait improvement in patients with a PPFG presentation. Our patient had progressive L-dopa resistant gait freezing and falls. Within days of PPN-DBS a marked improvement in gait was observed and he has had no falls since DBS surgery. He has required steady increases in his stimulation parameters, presumably as the underlying disease progresses, but has retained a stable improvement of gait now for over 14 months. In contrast Ostrem *et. al.* recently reported a case of PPFG with PPN-DBS with only modest gait improvement[14]. The reason for these discrepant findings may lie in the variable pathological basis PPFG, our case was atypical in having a history of slowly progressive gait compromise starting over a decade ago and no significant upper body parkinsonism to suggest PD, PSP or other parkinsonian syndromes. In addition, Ostrem et al. implanted the left PPN and then right 3 months later and when turned off at 6 months a modest benefit was retained[14]. In contrast, we implanted the PPN bilaterally and on each occasion the PPN stimulation was turned off the beneficial effects on gait were lost within minutes. These observations imply the ongoing value of continuous PPN stimulation and the absence of a significant washout period or a significant lesional effect in our patient.

Formal analysis showed PPN-DBS significantly improved many gait and standing balance parameters in our patient which were lost when stimulation was off. The PET scan demonstrates that PPN stimulation increased metabolic activity of the brainstem and cerebellum. The PPN has rich connection within the brainstem and with cerebellar hemispheres[5] and these findings indicate that activation of these connections is correlated with an improvement in gait and standing stability. Several groups have reported that AP and ML sway are independently controlled during stance and visual targeting, presumably via different but interacting neuronal circuits[15 16]. Our finding of

selective reduction of ML sway in resting stance raises the possibility that the anatomical pathways mediating ML sway and gait are both directly influenced by PPN activation. Therefore, we propose that PPN-DBS may be a useful therapeutic modality in non-parkinsonian PPFG and possibly other central gait and stance disorders.

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TABLE 1. Freezing of gait, and gait and falls questionnaire scores pre-operatively and at 10, 20, 28, 40 and 60 weeks after pedunculopontine nucleus deep brain stimulation.

	Pre-op	**10 weeks**		**20 weeks**		**28 weeks**		**40 weeks**		**60 weeks**	
IPG status	**No IPGs**	**Off**	**On**	**Off**	**On**	**Off**	**On**	**Off**	**On**	**Off**	**On**
GF-Q	39/64	-	13/64	-	13/64	-	13/64	-	14/64		14/64
FOG-Q	16/24	16/24	6/24	17/24	7/24	17/24	7/24	18/24	8/24	18/64	8/64

TABLE 2. Formal three-dimensional gait assessment and posturography assessments with pre-operative gait (6 trials) and post-operative gait (6 trials) and balance (3 trials) with PPN-DBS turned off and on.

Gait Assessment		Pre-Operative	Post-Operative		Significance
		-minus 4 months	Off stimulation	On stimulation	
Temporal Characteristics					
Cadence (steps/sec)		1.5 ± 0.0	1.4 ± 0.1	1.8 ± 0.1	**a, b**
Stance Phase (% cycle)		71.1 ± 3.1	72.3 ± 2.3	66.0 ± 1.8	**a, b**
Swing Phase (% cycle)		28.9 ± 3.1	27.7 ± 2.3	34.0 ± 1.8	
Single Support (% cycle)		53.6 ± 3.4	46.8 ± 2.0	60.9 ± 1.0	**a, b**
Double Support (% cycle)		46.4 ± 3.4	53.2 ± 2.0	39.1 ± 1.0	
Walking Velocity (cm/s)		63.9 ± 6.7	47.7 ± 3.9	86.2 ± 8.3	**a, b, c**
Gait Stability Ratio (steps/m)		2.4 ± 0.3	3.0 ± 0.2	2.1 ± 0.2	**a, b**
Spatial Characteristics					
Stride Length (cm)		83.1 ± 9.7	66.2 ± 4.4	96.0 ± 7.7	**a, b**
Step Width (cm)		14.3 ± 0.7	13.2 ± 2.0	13.2 ± 2.8	ns
Standing Balance – Firm Surface *(Only post-operative studies)*					
Eyes Open:	COP: AP	-	80.9 ± 24.7	41.1 ± 7.9	ns
	COP: ML	-	72.1 ± 18.3	29.4 ± 7.0	**b**
	COM: AP	-	48.2 ± 10.1	30.1 ± 6.9	ns
	COM: ML	-	49.8 ± 12.1	22.3 ± 10.7	**b**
Eyes Closed:	COP: AP	-	61.5 ± 16.9	37.4 ± 2.3	ns
	COP: ML	-	52.2 ± 12.1	33.3 ± 11.3	**b**
	COM: AP	-	43.4 ± 15.5	26.5 ± 1.8	ns
	COM:ML	-	42.5 ± 12.5	27.8 ± 12.8	**b**
ns.	No significant differences between assessments ($p > 0.05$)				
a.	Post-operative on-stimulation significantly different to pre-operative ($p \leq 0.05$)				
b.	Post-operative on-stimulation significantly different to post-operative off-stimulation ($p \leq 0.05$)				
c.	Pre-operative significantly different to post-operative off-stimulation ($p \leq 0.05$)				

Data shown are means (±SD) and were compared using paired sample t-tests. Pre-operative studies and off stimulation post-operative studies were similar except for mild, but significant slowing in gait. PPN-DBS on stimulation produced significant improvement in most gait parameters compared to both the pre-operative and off stimulation states. In addition, mediolateral but not anteroposterior standing balance was also improved post-operatively by PPN-DBS stimulation.

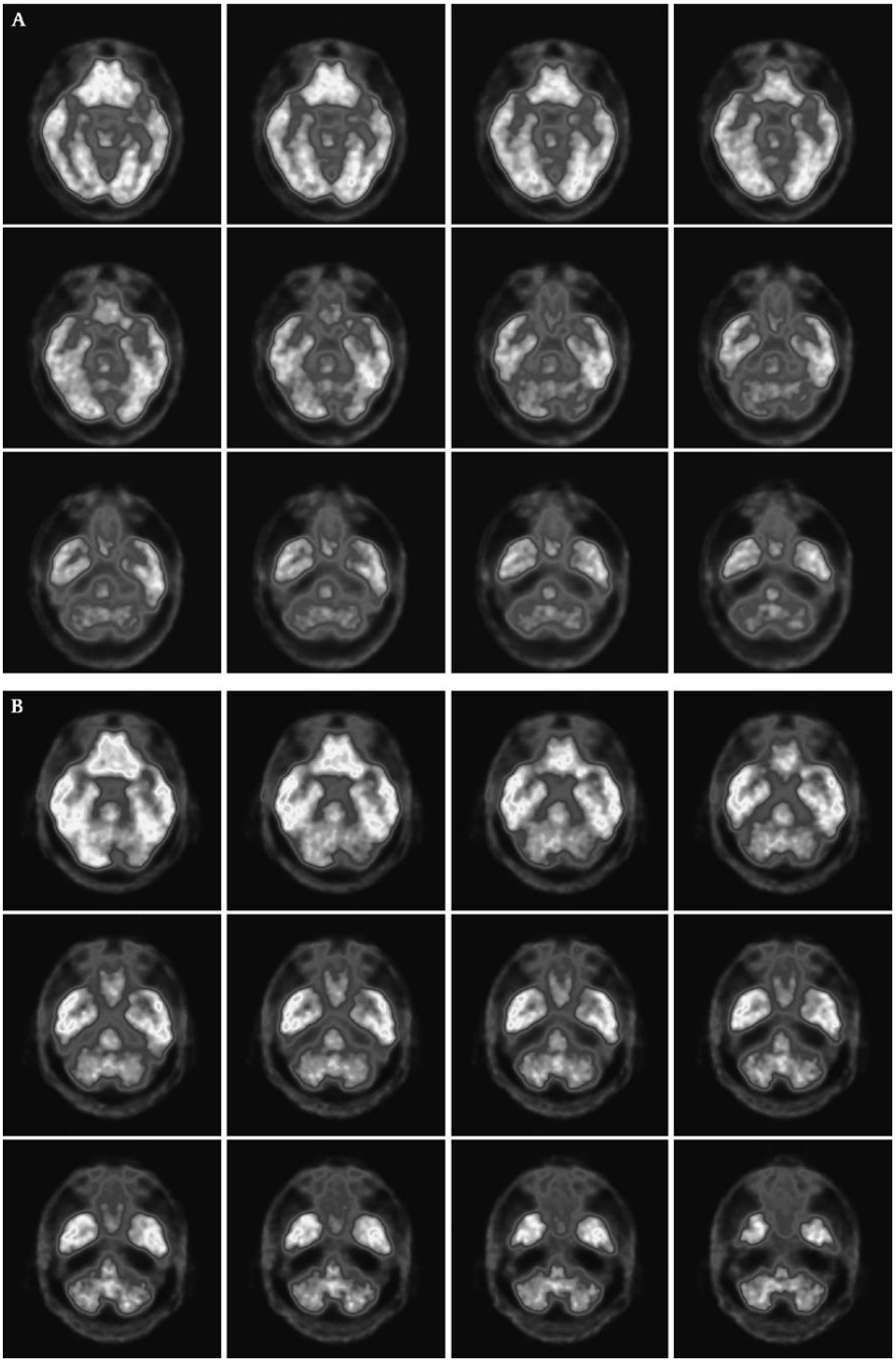

FIGURE 1. F-18FDG-PET studies performed with PPN-DBS stimulation turned off (A) and on (B). With both PPN-IPGs stimulators turned off, there was a pattern of diffusely decreased FDG uptake compared to normal brain, which was most prominent in the brainstem and both cerebellar hemispheres. With the PPN-IPGs turned on, there is a significant restoration of normal FDG uptake in the brainstem, cerebellar and probably the cerebral hemispheres.

Authors Roles

R Wilcox and T Coyne undertook the DBS procedure and post-operative clinical management. R Wilcox and P Silburn conducted clinical assessments. D Wong and R Wilcox undertook the PET study, and the PET images were reviewed by D Wong. M Cole, G Kerr and R Wilcox undertook the gait and posture analysis. All the authors contributed to the preparation of the manuscript.

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