Short report

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 (PPN) deep brain stimulation (DBS) as a treatment for primary progressive freezing of gait (PPFG).

Methods A patient with PPFG underwent bilateral 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 fluoro-2-deoxy-gucose positron emission tomography 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, cortico-basalganglionic degeneration, vascular Parkinsonism and postencephalitic Parkinsonism.1 However, it can present in association with normal pressure hydrocephalus and orthostatic tremor.1 3

The pedunculopontine nucleus (PPN) is a 5 mm 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 Pedunculopontine nucleus deep brain stimulation (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, 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 preoperatively, his FOG and postural stability worsened, he fell frequently, and he became increasingly chair- and bed-bound. The preoperative 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 there were 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 two or three 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 T MRI fluid-attenuated inversion recovery 1.0 mm contiguous axial slices were volumetrically fused (Stealth, Medtronic, Minneapolis) 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 brainstem and fourth 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 (Medtronic) implantable pulse generators (IPG) were placed under anaesthesia.10 Lead position was confirmed postoperatively via 1.5 T MRI.

Bilateral monopolar stimulation of the IPGs was commenced 24 h postsurgery 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-DBS12 with rates of 25–50 Hz and pulse widths of 60 μs. Slightly higher stimulation rates of 35 Hz were optimal in this patient and during the study were: right-IPG 3.5–3.8 V, 60 μs and 35 Hz and left-IPG 2.8–3.3 V, 60 μs and 35 Hz. If PPN stimulation was withdrawn, gait function deteriorated to essentially his preoperative state within 2 min (table 1). Fortunately, gait was restored within 2 min of reactivating PPN-IPG stimulation.
The patient found inactivation of his PPN stimulators very unpleasant and reported 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 preoperatively and postoperatively in various on- and off-states while optimising IPG parameters. The GF-Q and FOG-Q[^8] were used for pre- and postoperative comparison (0, 10, 20, 28, 40 and 60 weeks).

Formal gait assessment and balance were undertaken 4 months pre- and 10 weeks postoperatively. 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 (200 Hz) using a six-camera motion analysis system (Vicon, Oxford), which allowed calculation of temporospatial gait characteristics and the whole body centre of mass (COM).

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

Fluorine-18-deoxy-D-glucose (F-18FDG) positron emission tomography studies were performed 22 weeks after DBS surgery. Two segmented F-18FDG studies were performed 4 days apart with PPN-IPGs turned on and off. These were performed after intravenous administration of 500 MBq of F-18FDG using a dedicated Philips Allegro positron emission tomography scanner (Netherlands). For the off study, the IPGs were turned off for 50 min prior to the administration of F-18FDG. The images were reviewed using a visual analysis and displayed in a Rainbow colour format with a lower threshold of 0 and higher threshold of 8.

Table 1. Freezing of gait, and gait and falls questionnaire scores preoperatively and at 10, 20, 28, 40 and 60 weeks after pedunculopontine nucleus deep brain stimulation

<table>
<thead>
<tr>
<th>Implantable pulse generators status</th>
<th>Preoperatively</th>
<th>10 weeks</th>
<th>20 weeks</th>
<th>28 weeks</th>
<th>40 weeks</th>
<th>60 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gait and falls questionnaire</td>
<td>39/64</td>
<td>16/24</td>
<td>17/24</td>
<td>17/24</td>
<td>18/24</td>
<td>18/64</td>
</tr>
<tr>
<td>Freezing of gait questionnaire</td>
<td>16/24</td>
<td>16/24</td>
<td>17/24</td>
<td>17/24</td>
<td>18/24</td>
<td>18/64</td>
</tr>
</tbody>
</table>

Table 2. Formal three-dimensional gait assessment and posturography assessments with preoperative gait (six trials) and postoperative gait (six trials) and balance (three trials) with pedunculopontine nucleus deep brain stimulation turned off and on

<table>
<thead>
<tr>
<th>Gait assessment</th>
<th>Preoperative Minus 4 months</th>
<th>Postoperative On stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal characteristics</td>
<td>Cadence (steps/s)</td>
<td>1.5±0.0</td>
</tr>
<tr>
<td></td>
<td>Stance phase (% cycle)</td>
<td>71.1±3.1</td>
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<tr>
<td></td>
<td>Swing phase (% cycle)</td>
<td>28.9±3.1</td>
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<tr>
<td></td>
<td>Single support (% cycle)</td>
<td>53.6±3.4</td>
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<tr>
<td></td>
<td>Double support (% cycle)</td>
<td>46.4±3.4</td>
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<tr>
<td></td>
<td>Walking velocity (cm/s)</td>
<td>63.9±6.7</td>
</tr>
<tr>
<td></td>
<td>Gait stability ratio (steps/m)</td>
<td>2.4±0.3</td>
</tr>
</tbody>
</table>

| Spatial characteristics | Stride length (cm) | 83.1±9.7 | 66.2±4.4 | 96.0±7.7 | *† |
| | Step width (cm) | 14.2±0.7 | 13.2±2.0 | 13.2±2.9 | NS |

<table>
<thead>
<tr>
<th>Standing balance—firm surface (only postoperative studies)</th>
<th>Eyes open</th>
<th>COP: AP</th>
<th>COP: ML</th>
<th>COP: AP</th>
<th>COP: ML</th>
<th>COP: AP</th>
<th>COP: ML</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>80.9±24.7</td>
<td>72.1±18.3</td>
<td>48.2±10.1</td>
<td>49.8±12.1</td>
<td>37.4±2.3</td>
<td>52.2±12.1</td>
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<tr>
<td></td>
<td></td>
<td>41.1±7.9</td>
<td>29.4±7.0</td>
<td>30.1±6.9</td>
<td>22.3±10.7</td>
<td>37.4±2.3</td>
<td>33.3±11.3</td>
</tr>
</tbody>
</table>

Data shown are means (±SD) and were compared using paired sample t tests. Preoperative studies and off stimulation postoperative studies were similar except for mild, but significant slowing in gait. Pedunculopontine nucleus deep brain stimulation on stimulation produced a significant improvement in most gait parameters compared with both the preoperative and off stimulation states. In addition, mediolateral (ML) but not anteroposterior (AP) standing balance was also improved postoperatively by pedunculopontine nucleus deep brain stimulation.

*Postoperative on-stimulation significantly different from preoperative (p<0.05).
†Postoperative on-stimulation significantly different from postoperative off-stimulation (p<0.05).
‡Preoperative significantly different from postoperative off-stimulation (p<0.05).
COM, centre of mass; COP, centre-of-pressure; NS, no significant differences between assessments (p>0.05).
Fluorine-18-deoxy-D-glucose (FDG) positron emission tomography studies performed with pedunculopontine nucleus deep brain stimulation turned off (A) and on (B). With both PPN-IPG stimulators turned off, there was a pattern of diffusely decreased FDG uptake compared with 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.

Figure 1  Fluorine-18-deoxy-D-glucose (FDG) positron emission tomography studies performed with pedunculopontine nucleus deep brain stimulation turned off (A) and on (B). With both PPN-IPG stimulators turned off, there was a pattern of diffusely decreased FDG uptake compared with 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.
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 postoperatively. 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.

F-18FDG positron emission tomography studies with both PPN-IPG stimulators off were abnormal with a pattern of diffusely decreased FDG uptake compared with 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, cerebellum and 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.

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 5 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 that PPN-DBS significantly improved many gait and standing balance parameters in our patient which were lost when stimulation was off. The positron emission tomography scan demonstrates that PPN stimulation increased metabolic activity of the brainstem and cerebellum. The PPN has a 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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Competing interests None.

Patient consent Obtained.

Contributors RAW and TC undertook the DBS procedure and postoperative clinical management. RAW and PS conducted clinical assessments. DW and RAW undertook the positron emission tomography study, and the positron emission tomography images were reviewed by DW, MHC, GK and RAW undertook the gait and posture analysis. All the authors contributed to the preparation of the manuscript.

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REFERENCES


