Long-term follow-up of deep brain stimulation of pedunculopontine nucleus in progressive supranuclear palsy: Report of three cases

Domenico Servello, Edvin Zekaj, Christian Saleh, Claudia Menghetti, Mauro Porta

Abstract

**Background:** Progressive supranuclear palsy (PSP) is a neurodegenerative disease due to mitochondrial dysfunction. The PSP syndrome presents generally with gait disorder, Parkinsonism, ophthalmoparesis and cognitive alteration. Few reports exist on deep brain stimulation (DBS) in patients with atypical Parkinsonism. The aim of our study was to evaluate further the potential role of DBS in PSP.

**Case Description:** We report three patients with PSP with long-term follow up undergoing DBS. Two patients had right peripedunculopontine nucleus (PPN) stimulation and one patient had simultaneous right PPN and bilateral globus pallidus internus DBS. DBS of the PPN alone or combined with globus pallidus internus (GPI) determined an improvement in gait and a reduction in falls sustained over time. Combined target stimulation (GPI-PPN) was correlated with better clinical outcome than single target (PPN) DBS for PSP.

**Conclusions:** Although few data on DBS for PSP exist, reported clinical results are encouraging. DBS might be considered as an alternative therapeutic option for patients with PSP presenting with relevant gait imbalance and frequent falls, who fail to respond to pharmacological treatment. Larger cohorts with longer follow-ups are needed to evaluate more exhaustively the efficacy of DBS in PSP.

**Key Words:** Axial symptoms, deep brain stimulation, peripedunculopontine nucleus, progressive supranuclear palsy

INTRODUCTION

Progressive supranuclear palsy (PSP) is a neurodegenerative disease secondary to mitochondrial dysfunction characterized by neurofibrillary tangles accumulation and neurolipid threads in subthalamic nucleus, pallidum, red nucleus, substantia nigra, striatum, pontine tegmentum, oculomotor nucleus, medulla, and dentate nucleus.

The PSP syndrome classically presents with gait disorder, cognitive alteration, Parkinsonism, and ophthalmoparesis (vertical gaze palsy). A plethora of PSP phenotypes have been described.[25,26] PSP subtypes show different responses to levodopa: A moderate response is present in PSP-Parkinsonism (PSP-P), while classical Richardson’s syndrome has a poor response.[28] Also drugs acting at serotonergic, cholinergic, and noradrenergic
sites were tried.\cite{8} Rivastigmine has some positive effect on cognitive deficit in PSP.\cite{9} A small double-blind trial revealed that tricyclic antidepressants improved gait and rigidity.\cite{10} Botulinum toxin was used in PSP to treat dystonia.\cite{17,23} However, insufficient data does not allow any recommendation for a specific treatment in PSP. Few case-reports exist on deep brain stimulation (DBS) in patients with atypical Parkinsonism.\cite{6,15,16,33} We report our experience with DBS in three patients with PSP.

**Case 1**

A 70-year-old male patient with a diagnosis of PSP presented with gait imbalance and frequent falls. Levodopa and ropironolo were tried but provided only partial benefit. The neurological evaluation prior to surgery revealed vertical gaze paralysis, dysarthria, dysphagia, and left sided dysmetria. Deambulation was solely possible with the help of a caregiver. In light of his gait imbalance and frequent falls, we proposed DBS surgery of the rostral pedunculopontine nucleus (PPN). The patient underwent electrode implantation (Medtronic, Model 3389, Minneapolis, MN, USA) in the right PPN. The PPN region was located lateral to the superior cerebellar peduncle, its decussation and central tegmental tract and medial to the lemniscal system.\cite{32} The patient underwent volumetric brain T1 magnetic resonance imaging (MRI) and a MRI DPI sequence. Superior cerebellar peduncle and its decussation were directly visualized and the target was chosen lateral to these structures and medial to the lemniscal system.

Targeting occurred on T2-weighted MRI at the rostral part of the PPN between the superior cerebellar peduncle decussation and the lemniscal system.\cite{32}

Surgical procedure was uneventful. Two days after lead implantation, we performed a brain MRI [Figures 1-3], which confirmed correct lead position. We started with low frequency stimulation (35 Hz) that resulted in an improved postural stability. Progressively we increased the frequency of stimulation to 150 Hz with persistent clinical improvement. At one year follow-up, the patient reported a reduction in falls and an improvement in gait imbalance. The subjectively reported clinical improvement was associated with a 22% decrease on the progressive supranuclear palsy rating scale (PSPRS) [Table 1].

**Case 2**

A 68-year-old male patient presented with muscular hypertonus in the left superior limb of one year duration associated with dystonia in the left hand. Subsequently his clinical picture worsened with difficulty in deambulation and progressive gait enlargement. Neurological examination revealed further severe dysarthria and vertical gaze paralysis. The patient was able to walk only with bilateral sustain. In consideration of severe gait disturbances, DBS of the PPN was proposed. The patient underwent unilateral lead implantation (Medtronic, Model 3389, Minneapolis, MN, USA) in the right PPN [Figure 4]. The procedure was uneventful. Equally in this patient we started with low
frequency stimulation, which was progressively increased to high frequency stimulation, which resulted in gait improvement. The patient reported less assistance for daily activities. A 21% decrease on the PSPRS was noted at the 12 months follow-up visit [Table 1].

**Case 3**
A 66-year-old male presented with bradykinesia, ideomotor slowing, upward gaze palsy, and dystonia. In the previous months before admission at our department, a worsening of postural stability with frequent falls were observed. Dopaminergic therapy was poorly effective. Considering his strong dystonic component and difficulties in postural stability, the patient underwent DBS of the postero-ventral GPi and right PPN (Medtronic, Model 3389, Minneapolis, MN, USA). Implantation of both targets [Figures 5 and 6] occurred during the same procedure. At the one year follow-up visit his dystonia, gait, and postural stability had improved with a 36% reduction on the PSPRS [Table 1].

**DISCUSSION**
The PPN forms part of the rostral locomotor region of the brainstem.[3,4,22] Experimental evidence suggests that it plays a central role in the initiation and maintenance of gait.[3,7,18,19] The classical clinical picture of PSP presents most frequently with a symmetric, akinetic-rigid syndrome, vertical supranuclear gaze palsy, frontal deficits, prominent postural instability, and falls.[10,11,28,29] PSP responds poorly to pharmacological therapy. Considering that postural imbalance and falls are the most disabling symptoms in PSP, DBS of the PPN is considered in pharmacological refractory cases. Preferably DBS should be applied in the early stages of the disease when cognitive function is preserved.

Several authors reported DBS to the rostral brainstem in Parkinsonian patients.[2,6,14-16,21,24,27] These studies reported variable clinical results. The heterogeneity in clinical outcome might be related to the topographic variability of the PPN and the degree of atrophy of the PPN and damage of interconnected basal ganglia structures.[5,30,31] Further methodological diversity, such as single versus multiple target stimulation, targeting methods and consequently different anatomical location of implanted electrodes in the rostral brainstem may explain the different clinical results.[1,2,13]

**Table 1: Progressive supranuclear palsy rating scale (PSPRS)-IV scores pre-DBS, at 12 and 24 months**

| Patient | Target | PSPRS-IV pre DBS | PSPRS-IV at 12 months | PSPRS-IV at 24 months | % reduction at 12 months |
|---------|--------|------------------|-----------------------|-----------------------|-------------------------|
| No 1    | R-PPN  | 18               | 14                    | 14                    | 22.2                    |
| No 2    | R-PPN  | 15               | 11                    | -                     | 21.4                    |
| No 3    | R-PPN, bl GPi | 14          | 9                     | -                     | 35.7                    |

PPN: Peripedunculopontine nucleus, DBS: Deep brain stimulation, R: Right, GPi: Globus pallidus internus, bl: bilateral, No: Number, PSPRS: Progressive supranuclear palsy rating scale
Based on the preliminary reports on DBS in PSP, we decided to perform DBS in three selected patients with PSP, who presented as major disabling symptoms gait imbalance and falls with mild cognitive deficits.

We have chosen unilateral stimulation, based on previous work of Moro et al. and the extended experience of Mazzone et al., in which the authors obtained clinical improvement (i.e. falls, gait) with unilateral PPN stimulation. The site of implantation was chosen contralateral to the more compromised site of the body.

In all the three patients, a reduction of falls and an amelioration of postural balance were observed. The patients required less assistance for daily living activities. The clinical improvement was, however, not fully reflected in the evaluating scales. The mean PSPRS percentage decrease was of 26.3% (SD = 8.3) at the 12 months follow-up visit for the three patients. The diversity between the reported improvement and the PSPRS might be due to the phenomenological diversity of PSP, not fully captured by the PSPRS, and repeated scheduled postoperative evaluations are necessary to capture objectively the overall clinical improvement. That the greatest PSPRS percentage decrease (35.7%) was seen in the double implanted GPi-PPN patient is possibly due to the improvement of his dystonic state. It remains of course speculative in light of a single case, if this better clinical outcome seen in the GPi-PPN patient is reflection of an increased synergic effect of PPN and GPi secondary to stimulation, bearing in mind the strong connectivity between the basal ganglia and the PPN.

An interesting observation was related to the stimulation parameters; we started with low frequency stimulation, which was increased progressively to 130 Hz without noticing a significant change in clinical presentation.

CONCLUSION

Our three cases support further the role of DBS of the PPN in improving postural stability and reduction of falls over an extended time period. However, more data on DBS in atypical Parkinsonism is needed to evaluate further the efficacy of neuromodulation in PSP.

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