Clinical Experience with Pedunculopontine Nucleus Stimulation in Conditions with Nigrostriatal Disconnection

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■ BACKGROUND: **The pedunculopontine nucleus (PPN) is a part of the mesencephalic locomotor region and, in recent years, it has been considered a new surgical target for deep brain stimulation (DBS) for movement disorders including atypical parkinsonian syndromes such as progressive supranuclear palsy (PSP) and multiple system atrophy. Involvement of the PPN may play an important role in gait impairment in these disorders and the development of PPN DBS could potentially provide treatment for this disabling problem. However, the role of the PPN and the specific pathways involved in gait control and other motor functions are poorly understood.**

■ METHODS: **We present a chronological account of our group's experience in the use of PPN DBS. This entails the treatment of four patients with disabling movement disorders who all exhibited either marked damage or disconnection of the nigro-striatal pathway.**

■ RESULTS: **Within our series, the results were variable in that 2 of the 4 patients benefited greatly from DBS but the other 2 did not.**

■ CONCLUSIONS: **Our findings suggest that in carefully selected patients, PPN DBS can potentially alleviate symptoms due to dopaminergic striatal inactivity; symptoms that are typically resistant to stimulation of other subcortical targets used for parkinsonian syndromes and movement disorders.**

INTRODUCTION

This study concerns patient selection for, and the use of, pedunculopontine nucleus (PPN) deep brain stimulation (DBS), from both a structural/neuroanatomic and a physiologic/movement disorder point of view. It is a chronologic series of 4 cases, all showing marked damage or disconnection of the nigrostriatal path. We have reported these cases in this way to reflect our learning curve with this strategy. Within the series, results are variable; but 2 of the 4 patients have been functionally transformed, suggesting that for the right patient, with an understanding of what can be achieved, PPN DBS can be an invaluable strategy.

This report was prompted in part by the realization that we use PPN DBS to treat a different group of patients from that in the limited published clinical series, which have considered mainly Parkinson disease (PD)[1-4] and multiple system atrophy (MSA).[5,6] Furthermore, the results in these series have been variable, again raising issues of patient selection and our understanding of this target.

The background to this field stemmed from observations that the PPN degenerates in PD and progressive supranuclear palsy,[7-9] and in the parkinsonian primate model, subthalamotomy

Key words
- Nigrostriatal
- Parkinsonian
- Pedunculopontine
- Stimulation

Abbreviations and Acronyms
AC: Anterior commissure
BFMDRS: Burke Fahn and Marsden Dystonia Rating Scale
DAT: Dopamine transporter
DBS: Deep brain stimulation
GPi: Globus pallidus internus
MRI: Magnetic resonance imaging
MSA: Multiple system atrophy
PC: Posterior commissure
PD: Parkinson disease
PPN: Pedunculopontine nucleus
STN: Subthalamic nucleus
Vim: Ventrointermediate nucleus of the thalamus

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improves signs and symptoms and activates the PPN. This led to the demonstration that directly activating the PPN in the same model (either by low-frequency electrical stimulation or neurochemically by gamma aminobutyric acid blockade) improved parkinsonian features, including hypokinesia, axial stability, and gait.[10] That these effects are mediated via a nondopaminergic pathway[11] raised the possibility that nondopamine responsive symptoms in PD, such as gait instability and falls, might be alleviated by PPN DBS, and that this might also help other nondopamine responsive parkinsonian conditions such as MSA. The neuroanatomic and pathophysiologic basis, and hence rationale for this therapeutic intervention, have been described in more detail elsewhere in the literature.[12]

Reflecting this hope, several groups have published limited clinical series. The Oxford group, based on their work with the primate model, used PPN DBS in PD in the unusual circumstance of patients in whom gait freezing was the predominant symptom, with good effect,[4] and a similar approach was used by the Toronto group.[13] Two groups, Bristol [2,14,15] and Grenoble,[16] have attempted to combine DBS of the subthalamic nucleus (STN) and PPN. Although notionally attractive in trying to alleviate both dopamine-responsive and -unresponsive symptoms, the interactions between the 2 nuclei may add to the complexity, compromising the choice of stimulating frequency, with a consequent loss in the efficacy of stimulation.

Our own approach has been different and has been based less on progressive neurodegenerative conditions and more on patterns of established anatomic damage and dysfunction. This was prompted by a patient with an unusual movement disorder and a striking pattern of neostriatal damage, which first allowed us to explore human PPN stimulation responses. Over the subsequent 4 years, we have carried out a further 3 PPN DBS implants, in 1 case combined with bilateral globus pallidus internus (GPi), and in 1 bilateral thalamic ventrointermediate (Vim) electrodes. All 4 patients had profound loss or functional disconnection of the striatum and consequently were totally nonresponsive to dopamine. Although our clinical results have been variable, these patients have previously been untreatable, and 2 have had striking and gratifying responses. Because individual patient phenomenology was so variable and difficult to define, direct comparison using established disease-specific rating scales[17-19] was not possible. Patient presentations and clinical outcomes are therefore described in detail within each case vignette, even although the results of individual objective scores are included in the results section. Here, we summarize the evolution of our clinical experience and our current understanding of the PPN as a new DBS target for movement disorders.

METHODS

Surgery

Cases were discussed with and approved by the hospital clinical ethics board, and fully informed consent was obtained from the patients (in case 2 [a child], her parents) and family members, emphasizing the experimental nature of PPN stimulation. Surgery was performed under general anesthesia, using the Cosman-Robert-Wells frame, targeting with previously acquired magnetic resonance imaging (MRI) scans fused to a stereotactic computed tomography scan. A more detailed account of the surgical methodology used has been described previously.[20,21] The imaging sequences used evolved during the time course of this series. Although there is no distinct classic MRI contrast to delineate the PPN from the adjacent brainstem structures, it is interposed with the decussation of the superior cerebellar peduncle medially and the medial lemniscus laterally. Initially, high-resolution diffusion tensor imaging was used to generate color fractional anisotropy maps to define the differing directions of these fiber tracts (Figure 1). Concern that this required echoplanar imaging and could have inherent anatomic distortions led us to use fat-suppressed T1-weighted images to define these structures[22,23] (Figure 2). Medtronic 3387 electrodes were implanted and their positions confirmed with stereotactic computed tomography scans (Figure 3), the target point also being related to the anterior commissure (AC)-posterior commissure (PC) line. Electrodes were connected to Kinetra 7428 batteries in 3 cases and to an Activa SC in 1 case (Medtronic Inc., Dublin, Ireland). Additional pallidal and thalamic electrodes were sited as part of the same procedure in the second and fourth cases.

Case Series

Table 1 summarizes the essential clinical features of the patients described in the case series. The individual patients are

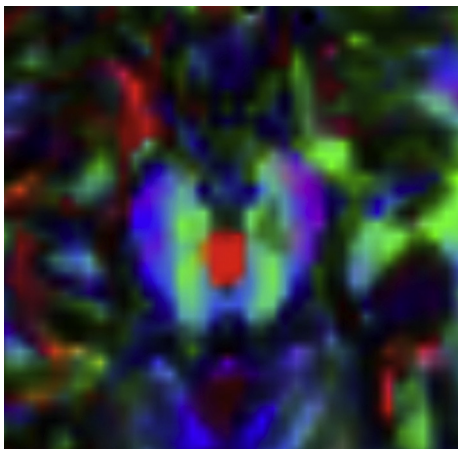

Figure 1. Color fractional anisotropy map through the lower mesencephalon at the level of the decussation of the superior cerebellar peduncles. The color image demonstrates the direction of fiber bundles generated from a diffusion tensor image. The standard color convention is red for left to right/right to left fibers; green for anterior to posterior/posterior to anterior fibers; blue for superior to inferior/inferior to superior fibers. The crossing fibers of the decussation of the superior cerebellar peduncle are therefore the central red area, the ascending medial lemniscus is the lateral blue area, and the largely posteriorly oriented fibers of the superior cerebellar peduncle are green. The pedunculopontine nucleus cannot be identified as a separate structure, but its location can be inferred from these regions where the fiber bundles are oriented in different directions.