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CASE REPORT

Improvement of hand dexterity induced by stimulation of the peduncolopontine nucleus in a patient with advanced Parkinson's disease and previous long-lasting bilateral subthalamic DBS

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Abstract We report the case of a patient already submitted to bilateral deep-brain stimulation (DBS) of the subthalamic nucleus (STN) who started to develop gait impairment, postural imbalance and frequent falls in the course of the disease and who subsequently underwent DBS of the right pedunculopontine nucleus (PPN) at our institute. An immediate clinical benefit in hand dexterity was observed with acute external stimulation and maintained after the definitive implant of the internal pulse generator (IPG) at 6 months' follow-up. The benefit on hand dexterity seemed to be related to the interactions between the PPN low-frequency stimulation and the bilateral STN high-frequency stimulation.

Introduction

The role of the pedunculopontine nucleus (PPN) in the control of gait and voluntary movements has been demonstrated in experimental primate models, suggesting its therapeutic application since 1998 [1].

PPN chronic stimulation in man was patented in the USA in 2002 by Lozano and Rise [4] but the first implants in human beings was published by Mazzone et al. [6] and by Plaha and Gill [10], who reported their work in the same issue of *Neuroreport* in 2005.

Nevertheless, the clinical research on PPN is still in a preliminary stage and the available published series suggest applications aimed at improving gait and axial symptoms in advanced Parkinson's disease [2, 9, 12]. PPN stimulation has been used in patients affected by Parkinson's disease with previous subthalamic nucleus (STN) implants or as a stand-alone application in patients with Parkinson's disease whose gait and posture impairment were the prevailing symptoms [7, 11].

We describe a patient with Parkinson's disease who had been harbouring a bilateral STN implant for 8 years and who, after acute and chronic PPN stimulation, obtained marked improvement of hand dexterity bilaterally. An appropriate evaluation scale for hand dexterity (DASH) [3] and another scale for quality of life (SF 36) were applied, together with the conventional Unified Parkinson's Disease Rating Scale (UPDRS) evaluation.

This case report suggests a clinical application of PPN stimulation not only targeted for gait and for freezing but also for the possibility of obtaining further clinical improvements in patients with a long-lasting disease who have had benefits from STN DBS.

Case report

This 66-year-old woman, a Roman Catholic nun, started to complain of tremor and bradykinesia of the right side about 10 years before admittance to our institute. After the diagnosis of Parkinson's disease was made, the patient started treatment with levodopa with mild improvement of bradicinesia and rigidity, but without improvement of right upper limb tremor. In 2001 she underwent unilateral left STN deep-brain stimulation (DBS), with an 80% improvement on the UPDRS motor sub score and the disappearance of tremor of upper right limb. Three years later, tremor also

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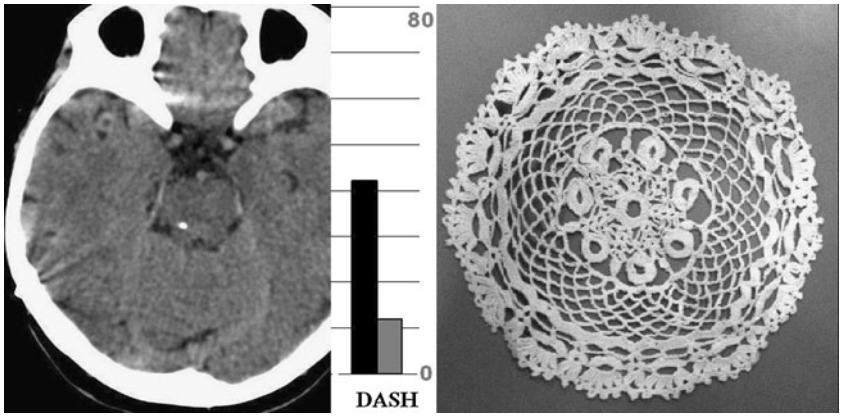

Fig. 1 *Left*: CT scan showing the tip of the deep-brain electrode, placed in the following coordinates (X 5, Y −18, Z –15) with respect to the midcomissural point. In the *middle* of the diagram is the DASH score that revealed an amelioration of the hand dexterity (*black* preop, *grey* follow-up). *Right*: a photograph of a crocheted lace doily made by the patient after surgery

appeared on the left hemibody and the patient was subsequently submitted to right STN DBS that resulted in control of controlateral tremor.

In the following years the patient presented progressive worsening of gait, with onset of postural imbalance and daily falls. Furthermore, hand dexterity gradually diminished, and the patient also started to complain of not being able to perform normal daily activities, such as cooking, dressing and needlework. The worsening of hand dexterity was mainly due to progression of upper limb's distal bradykinesia. These symptoms were refractory to both modification of drug therapy and of stimulation parameters. In 2010, DBS of the right PPN was performed, aimed at reducing postural imbalance and falls [7, 11]. Surgical intervention was performed under local anaesthesia; with the Leksell frame (Elekta, Stockholm, Sweden) computerized tomography (CT) exam scan in stereotactic conditions being performed for the targeting procedure. We also used the probabilistic Franzini atlas, updated with a specific program for PPN (www.angelofranzini.com/BRAIN.HTM). We took into account a previously published manuscript by Zrinzo et al. [13] about the position of the PPN relative to the anterior commissure-posterior commissure (AC-PC) line and the ventricular floor line (VFL). The definitive coordinates relaive to the midcomissural point (MCP) were: 5 mm lateral from the midline, 18 mm behind the mid-commissural point along the AC-PC line, and 15 mm below the MCP.

The definitive electrode (3389, Medtronic) was positioned after macrostimulation at the target site that elicited contralateral sensory responses (consistent with PPN's proximity to the medial lemniscus) with stimulation at 3 V, 30 Hz, 90-μs pulse width, monopolar mode.

In the following days the stimulation parameters were tested through an external stimulator, and finally set to 25 Hz, 60 μs and 2 V. Acute stimulation induced immediate improvement of hand dexterity, witnessed by the regained

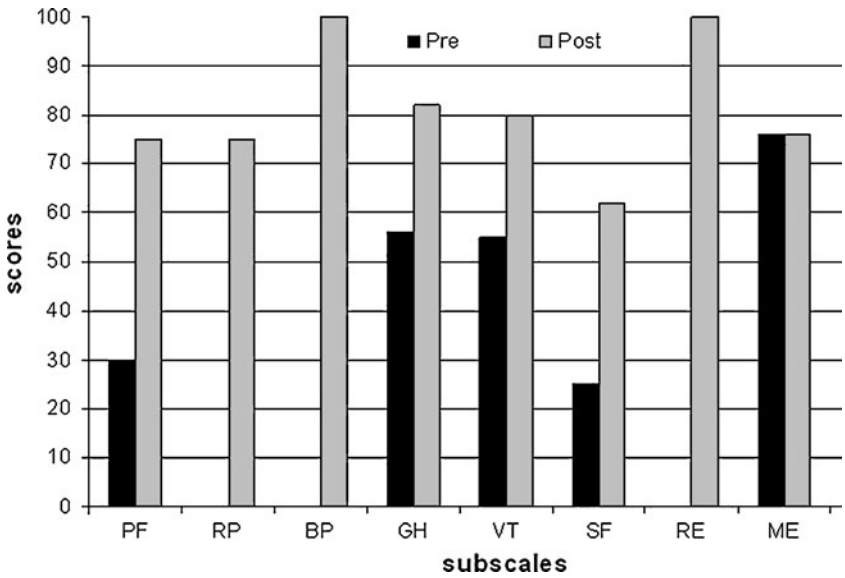

Fig. 2 Preoperative and postoperative subscores of SF 36 scale relative to last clinical follow-up (6 months). *PF* physical functioning, *RP* role limitations due to physical problems, *BP* bodily pain, *GH* general health perceptions, *VT* vitality, *SF* social functioning, *RE* role-limitations due to emotional problems, *ME* mental health

ability to create beautifully executed needlework (Fig. 1). The patient was unaware of the beginning of the electrical stimulation and no subjective sensation was reported during the acute turning on and off of the stimulator .

A few days later, the patient underwent, in general anaesthesia, a surgical procedure of positioning of an internal pulse generator (Soletra, Medtronic), which was connected to the deep-brain PPN electrode. Gait instability and postural imbalance were significantly reduced from the first week of definitive stimulation . In a few days, the patient also reported a significant reduction of the number of falls.

The patient was re-evaluated at follow-up 6 months later. The DASH score and the quality of life evaluation scale (SF 36) were applied together with the conventional UPDRS evaluation. A stable improvement in overall DASH score was noticed. The UPDRS scale part III improved from 29 to 15. Finally, the quality of life score also improved as assessed by the SF 36 scale (Fig. 2); this positive outcome on the quality of life was mainly due to improvement of the dexterity of the hand, which allowed the patient to perform several activities which were not possible before PPN DBS.

Discussion

This case confirms that PPN DBS should be taken into account as an adjunctive therapeutic option in the hands of trained neurosurgeons and neurologists involved in the treatment of movement disorders. In the literature, a small series of patients who underwent bilateral or unilateral electrode implantation within the PPN to improve freezing, gait, posture and axial symptoms in Parkinson disease [4, 6] have been reported. Also, in this specific case, the aim of the PPN implant was the improvement of gait and the reduction of falls; however, the clinical results not only achieved this goal but also an unexpected improvement of bilateral hand dexterity appeared acutely when the stimulator was turned on. This effect is chronically maintained by the PPN stimulation. The patient spent most of the day praying and making crocheted doilies and small pieces of needlework. For many years, about 80% of her finalistic movements concerned the hands, and the disease progressively slowed fine finger movements without real impairment of any specific movements, which were all possible but slow. The role of the concomitant STN stimulation is evident by the fact that when we turned off the STN IPG (unilaterally and/or bilaterally), most of the improved hand dexterity effect was lost. When we turned off the PPN IPG we immediately and completely lost the hand dexterity effect even, if STN DBS was still on. It is very difficult in a single case to explain this bizarre interaction between brainstem and mesencephalic nuclei involved in the control of movements. The PPN has a potential role in modulation of the basal ganglia output structures and of spinal neurons (with which it harbours bilateral connections), although most of the data available refer to studies on non-human primates, rodents and cats [8]; PPN neurons have been shown to modify their firing rates in response to movements of contralateral and ipsilateral arm in normal monkeys [5], and to voluntary and passive movements of both upper and lower limbs in humans [12]; it is then possible that the modulatory role of this nucleus is not limited to neuronal pathways involving the lower limbs.

We have only performed two implants of deep-brain electrodes into the PPN target so far; the other one was implanted as a stand-alone target (monolateral implant, right side) in a patient affected by iatrogenic Parkinson's disease (because of long-term use of neuroleptic drugs), whose main symptom was postural imbalance and appendicular tremor, and not hand dexterity.

We may comment that STN DBS gave the presented patient about a decade of well being and autonomy, and now PPN stimulation has given an additional chance to this woman, who would otherwise be condemned to worsen and to progressively lose her motor and creative abilities. In this report we suggest to add to the conventional UPDRS evaluation the use of other evaluation scales aimed at evaluating functions, such as hand dexterity and the quality of life, as in this case.

Conflicts of interest None.

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