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BRIEF COMMUNICATION

Successful subthalamic stimulation, but levodopa-induced dystonia, in a genetic Parkinson's disease

Alessandro Stefani · Francesco Marzetti · Mariangela Pierantozzi · Simona Petrucci · Enrica Olivola · Salvatore Galati · Mario Stampanoni Bassi · Paola Imbriani · Enza Maria Valente · Francesco Saverio Pastore

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Abstract Recently, it is under scrutiny the possibility to anticipate the stereotactic implantation of the subthalamic nucleus (STN) even in relatively mild Parkinson's disease (PD) patients with an unsatisfying response to drugs. In addition, it is debated whether levodopa (LD) and deep brain stimulation (DBS) are congruent or, instead, mutually exclusive. A 56-year-old LRRK2-positive PD patient, with 7 years of disease history, dominated by severe left resting tremor, was submitted to bilateral implantation of the subthalamic nucleus (STN). Before surgery, the combination of LD and dopamine agonists failed to handle tremor unless administered at doses, which induced undesirable adverse events. STN deep brain stimulation (DBS) abolished tremor but did not provide satisfying control of hypokinetic-rigid symptoms. The condition STIM-ON plus LD, albeit transiently beneficial, installed a painful dystonia developing slowly after 24–36 h. Only a chronic therapy combining rotigotine plus STN-DBS proved effective without side effects. This case report, based upon the surprising difference between the therapeutic response to the combination of LD and dopamine agonist (before surgery) and the combination of DBS and agonist after surgery, emphasizes how STIM and LD target different motor domains through mechanisms with differential plasticity and confirms the efficacy of STN-DBS in LRKK2 patients.

Keywords Deep brain stimulation · Dardarin · Parkinson's disease · Levodopa

A. Stefani · M. Pierantozzi · P. Imbriani
IRCCS Fondazione S. Lucia, Rome, Italy

A. Stefani (✉) · M. Pierantozzi · E. Olivola · M. S. Bassi
Department of Neuroscience, Movement Disorder Center, University of Rome Tor Vergata, Rome, Italy
e-mail: stefani@uniroma2.it

F. Marzetti · F. S. Pastore
Department of Neuroscience, Stereotactic Neurosurgery Unit, University of Rome Tor Vergata, Rome, Italy

S. Petrucci · E. M. Valente
Neurogenetics Unit, Mendel Laboratory, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy

S. Galati
Neurocenter of Southern Switzerland, Lugano, Switzerland

E. M. Valente
Department of Medical and Surgical Pediatric Sciences, University of Messina, Messina, Italy

We report on a 56-year-old Caucasian male with a 7-year history of Parkinson disease (PD) dominated by severe resting tremor, most pronounced in the left side, and moderate hypokinetic-rigid symptoms. Patient was first admitted to our Movement Disorder Centre in January 2010 under treatment with l-dopa (LD)/carbidopa (100/25 qid) plus pramipexole 3.0 mg/day. His clinical disability, quantified by the motor examination section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) was 12 at the "best on" condition and 27 at the practically defined "off" condition [after an overnight therapy withdrawal (Core Assessment Program for Intracerebral Transplantations)-CAPIT-] (Table 1).

In the last 3 years, clinical motor syndrome included occasional (weekly) dystonia-like brief (20–40 s) curling of the toe or plantar flexion of the left foot. The non-motor profile was unimpressive: neither sleep disorders, including RBD, nor hyposmia was detected, but only mild gastrointestinal symptoms were recognized at the NMSQuest [1]. The patient reported that his mother, died in her nineties,

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Table 1 The table illustrates mean UPDRS scores, distinguished in pre-surgery and different post-surgery epochs

Pre-surgery		Post-surgery		
	MED-OFF/ON	STIM-OFF/ON 1 month	STIM-OFF/ON 3 months	STIM-ON/MED-ON
UPDRS I (1–4)	0/0	0/0	0/0	0/0
UPDRS II (5–17)	6/3	5/1	5/1	5/1
UPDRS III (18–31)	27/12	24/7	25/8	25/5[a]

Presented are score in OFF therapy versus either MED-ON alone or STIM-ON or STIM-ON plus MED-ON

[a] At time of first hospital discharge, before the development of dystonia-like discomfort

suffered from PD. After obtaining written informed consent, we sequenced exon 41 of the LRRK2 gene in the patient's DNA [2] and found that he was heterozygote for the p.G2019S mutation, the most frequent monogenic cause of PD, with a frequency of about 1.8 % in the Italian population [2].

Since 2009, patient manifested impairment of postural stability and a progressive worsening of resting tremor, not adequately responsive to levodopa (LD). Hence, despite the relatively short clinical history, he manifested a strong wish to undergo stereotactic neurosurgery. Therefore, the patient started a careful protocol including 3-tesla MRI, cognitive evaluation, and a dose–response curve to LD doses up to 400 mg (Fig. 1a). Only supra-maximal LD doses (300 mg) suppressed tremor, but promoted moderate oro-facial, proximal left arm peak-dose dyskinesia and/or severe neuro-vegetative side effects (Fig. 1a).

Neurosurgery was performed in two sessions, 3 weeks apart, at the University of Rome Tor Vergata (Medtronic 3389 electrodes, Activa RP impulse generator, Medtronic Corporation, Minneapolis, MN, USA). Our standard procedure [3] implies stereotactic CT images merged with the preoperative magnetic resonance images (T1 and fast spin-echo inversion recovery sequences with double dose of contrast agent) and a second computation of the target coordinates performed with the neuronavigation system. Definitive coordinates were (with respect to mid-commissural CA–CP line) $X = \pm 11.3$; $Y = -3.5$; $Z = -3.4$.

Since completion of the whole surgical procedure (June 2010), the patient underwent a standard reglage. The more dorsal right catheter contact recruited oral spasms (threshold at 1.9 and 1.5 V) suggesting the involvement of corticospinal tracts [4]. The condition STIM-ON (contacts 2 and 8, 2.1 and 2.2 V, respectively, 180 Hz, pulse width 60 μs) MED-OFF was effective and maintained for about 3 months (Table 1). Yet, a residual left rigidity, the need to maintain a balanced mood and, not last, the fact that the patient lived 300 miles away induced us to reinstall a constant dose of LD, albeit lower than pre-surgery phase. Patient was dismissed with bilateral monopolar STIM (as above) together with LD 100 mg tid, plus rasagiline 1 mg/day and no dopamine agonists.

Unfortunately, despite an optimal control of tremor as well as hypokinetic-rigid symptoms, patient was suddenly back to the clinic due to the occurrence of a disabling dystonia-like pattern including neck pain and harmful contraction of left shoulder and proximal arm.

At first, a post-surgery MRI was performed to exclude gross mistargeting; then, a new "contact by contact" examination of STIM parameters, including the interleaving approach [5], was done under OFF-MED, in the early morning. As a result, contacts 2 and 8 (2.0 V, 180 Hz, 60 μs pulse width) were re-confirmed as the best monopolar contacts and the best parameters to use (large bipolar or double mono-polar STIM clinically unsound). As clarified in Table 1 and Fig. 1b (0 LD mg), STIM-ON alone produced a complete control of tremor and a discrete effect on bradykinesia. Incidentally, it is worth noticing that increase of STIM voltage above 2.4 V had a negative impact on language, in form of dysarthria.

Thereafter, a two-week observation period was dedicated to study the STIM-ON condition in different pharmacological assets (MED-OFF vs MED-ON, in form of increasing LD daily dosages) (Fig. 1b). This procedure allowed confirming that left dystonia, negligible on the first day (Fig. 1b), developed on the second/third day of STIM-ON/MED-ON condition. Indeed, during chronic LD therapy, painful dystonia occurred even at the lowest LD daily doses (Fig. 1c), becoming maximal around the expected pharmacokinetic peak of the drug (60–100 min) and extremely disabling.

We found that only the full LD withdrawal, substituted by the dopamine agonist rotigotine provided a reliable relief from dystonia (Fig. 1d). The final therapeutic option (since December 2010) is rotigotine (12 mg/day) plus the constant delivery of monopolar (contacts 2 and 8, respectively) STN-DBS with 2.1 V, 180 Hz, 60 ms pulse width. Since the last controls (June 2010), STIM has been increased up to 2.7 V. In terms of non-motor clinical spectrum, the patient has been manifesting similar profile with respect to the pre-surgical period. More importantly, no cognitive alterations occurred. Longer follow-up is required to judge if the present combined therapy is changing his

psychological attitude (so far, only an occasional altered copying toward a specific stressful event was recorded; rarely, a hypnotic was administered night-time).

Our case confirms how monopolar DBS stimulation at low amplitude, in contrast with LD at sub-maximal doses, reveals a peculiar efficacy in suppressing rest tremor through instantaneous de-synchronization of neural activity in sub-cortical structures and/or antidromic resetting of motor cortex. Conversely, STIM alone was not appropriate to handle efficaciously hypokinesia. Further, a stable LD regimen plus STIM-ON, although providing a good fast relief of PD signs (Fig. 1b), promoted slowly (1–2 days to reach the acme) a painful left dystonia forcing an unconventional optimization of treatment (Fig. 1d). Only the full LD de-titration (and its substitution with DA-agonist) endorsed the inhibition of the disturbing proximal dystonia.

The adverse event was relatively dose-dependent under STIM-ON, since the patient manifested the higher discomfort at the peak of each LD dose absorption, as expected given the LD pharmacokinetic profile. The observed discomfort is, in our opinion, not related to the coexistence of a capsular-like effect [4]. The stimulation of the more dorsal right catheter contact induced the occurrence of oral spasms, suggesting the involvement of corticospinal tracts; however, such an acute recruitment, under STIM, of *viciniori* pyramidal tract fibers has nothing to share with a slowly developing deterioration of motor performance as here described.

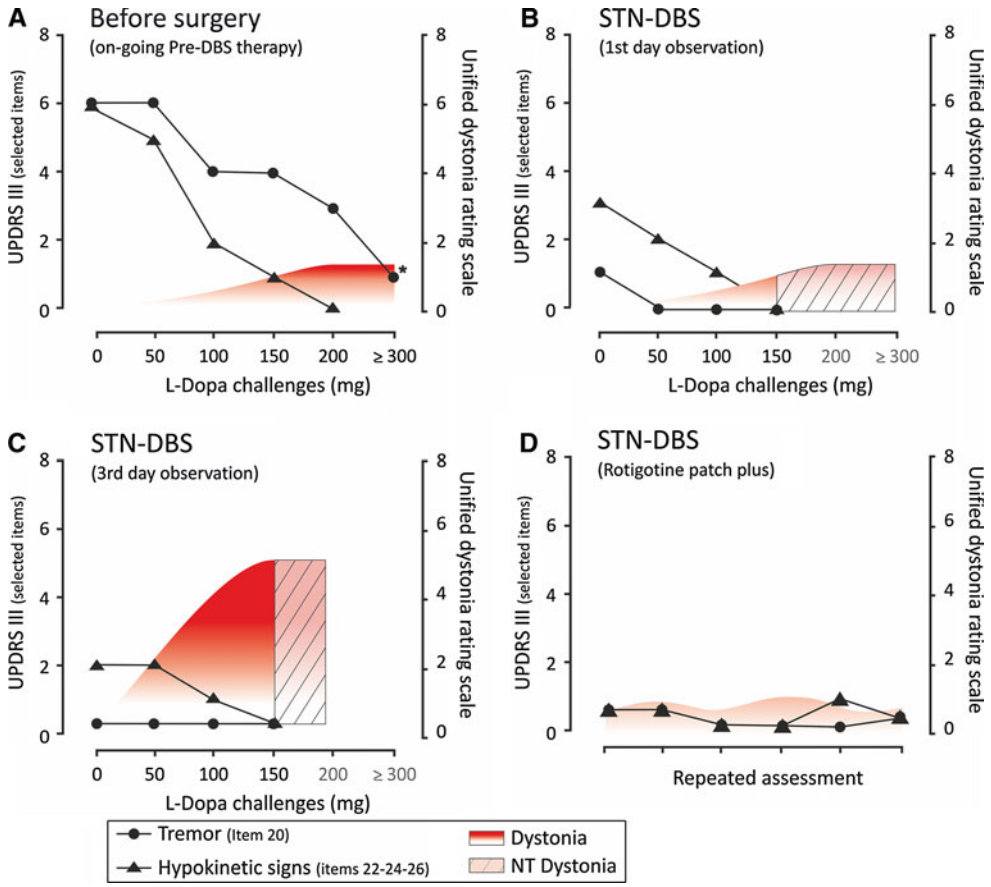

Fig. 1 Shown are the motor scores in response to different LD acute challenges in different clinical phases. **a** Defines pre-surgical phase (March 2010); **b** and **c** describes post-surgical phase (September 2011); **d** depicts the present follow-up (since summer 2011). **a** Exemplary response in the pre-surgery phase. Sub-maximal LD doses do not provide substantial control of tremor; only 300 mg abolished left rest tremor but the patient suddenly experienced a lipothymia (* in A). **b** Note the transient full benefit of the condition STIM-ON MED-ON (first day therapy). **c** STIM-ON MED-ON 2 days later with the disturbing dystonia-like pattern. **d** Shown are the motor scores in response during a stable therapeutic regimen, which includes STN-DBS plus transdermal rotigotine. *X* axis represents different LD doses. *Left Y* axis represents the mean score (sum of the two left arms) of specific UPDRS items (as indicated in the legend). *Right Y* axis is a quantification of the dystonia-like impairment utilizing the Unified Dystonia rating scale (UDRS) [10]. To note, this scale was proposed originally for dystonic patients (analogously to the global dystonia and the Fahn–Marsden scales) but it is peculiarly useful here to describe our subject since it combines a motor severity factor with a duration factor. For example, under 100 mg LD the UDRS score reaches 4 (in **c**) as a product of the duration factor 2 ("intermittent and mostly sub-maximal") and the intensity factor 2 ("moderate"). *NT* not tested

Instead, in our case the association LD-STIM was responsible of a dystonia-like phenomenon, possibly dependent upon a reorganization of cortically driven striatal LD-dependent abnormal plasticity [6]. Not surprisingly, the good tolerability toward a stable pharmacological regimen with the rotigotine patch indicates that a smooth binding to widespread D2-like receptors minimizes the risk of unmasking LD-related involuntary movements, otherwise propelled by LD. The persisting efficacy of rotigotine, so far and the lack of disabling dyskinesias despite the titration up to 12 mg may indicate that with respect to levodopa, the dopamine agonist exerts a minor effect on the endogenous "indirect circuit" and the D1-bearing medium spiny neurons, which govern the striato-pallidal pathway. In this content, the specific effect of rasagiline is difficult to evaluate, since not in place before surgery.

Whether the association DBS-LD is known to increase peak involuntary movements in several PD patients (and of course as an acute complication of misplaced electrodes), we are not aware of cases similar to this presently shown. Previous descriptions seem to be confined to a single patient affected by a juvenile dystonia-parkinsonism form worsened by LD [7].

Our patient, pre-DBS, had presented quite brief and distal atethotic-like dystonia features in the left foot and, occasionally, grimaces during LD peak. Whether his genetic profile (LRRK2 positive) made him more vulnerable to LD-mediated involuntary movements [8] or candidates him to some deleterious reorganization of corticostriatal efferents modulated by STIM-ON remains to be understood in full.

STN-DBS was proved effective already in PD patients with analogous mutation, although limited series are available so far [9]. The efficacy of STN-DBS in LRKK2 patient as ours sounds promising in extending the surgical indication to the first decade of clinical history.

In conclusion, our study supports the notion that, in PD patients with complex clinical phenotype, DBS and LD may target different motor domains and do not exert, a priori, additive roles. Here, in particular, LD- and STN-DBS-mediated effects were mutually exclusive and forced an unconventional therapeutic recipe.

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Conflict of interest No conflict of interest by any author.

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