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Original Article

# Emergence of restless legs syndrome after subthalamic stimulation in Parkinson's disease: a dopaminergic overstimulation?

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ABSTRACT

*Objective:* Studies investigating the effects of subthalamic deep-brain stimulation (DBS-STN) on restless legs syndrome (RLS) in Parkinson's disease (PD) are limited and report conflicting results, with some describing the emergence of RLS after DBS-STN, while others report postoperative improvement of this disorder. Severe decrease in postoperative dopaminergic medications dose, which may unmask RLS symptoms, has been proposed to explain the emergence of RLS after surgery. We aimed to specifically identify factors associated with the risk of developing RLS after DBS-STN in order to enhance our comprehension of the underlying mechanisms contributing to the development of RLS in PD.
*Patients:* In this observational prospective study, we evaluated the occurrence of RLS in 31 patients with PD originally free from RLS symptoms, six months after bilateral chronic DBS-STN, and compared clinical and treatment parameters of patients who developed postoperative RLS with those of patients without postoperative RLS.
*Results:* Six patients out of 31 reported post-operative emergence of RLS. There was no between-group difference in demographic data, pre-operative treatment parameters or clinical improvement measures after DBS-STN. However, PD patients with emergence of RLS after DBS-STN had a higher dose of dopamine agonists at postoperative evaluation compared to PD patients without emergence of RLS ($p = 0.040$) and a lower percentage of decrease in dopamine agonists ($p = 0.043$).
*Conclusion:* Overstimulation resulting from cumulative effects of dopamine agonists and STN-DBS may induce changes in excitability of the dopaminergic system, leading to an emergence of RLS. Clinicians should take into account this phenomenon while adjusting pharmacological treatment after surgery.


## 1. Introduction

Restless Legs Syndrome (RLS) and Parkinson's disease (PD) are both common neurological disorders involving an impaired central dopaminergic transmission [1]. Moreover, RLS has been reported to be more frequent in PD than in the general population [2–5], though this association is still being discussed [6–9]. Thus, the hypothesis of a common etiological link between these two diseases has emerged and remains a current matter of debate.

Subthalamic deep-brain stimulation (DBS-STN) is a well-documented treatment for severe PD with motor fluctuations and levodopa-induced dyskinesias (LIDs), allowing a dramatic improvement of motor symptoms and a reduction in Levodopa equivalent daily doses (LEDD) [10]. Knowing that dopaminergic agents that are used to treat Parkinson's disease represent the treatment of choice for RLS [11], an improvement of RLS in PD patients after DBS-STN could also be expected. Yet, studies investigating the effects of DBS-STN on RLS in PD are limited and report conflicting results, with some of them actually describing emergence of RLS after DBS-STN [12], and others reporting improvement after surgery [13,14]. It has been hypothesized that RLS after DBS-STN could be due to the postoperative decrease in dopaminergic medications, which may unmask RLS symptoms [12]. However, RLS was found to improve after DBS-STN in other studies, despite a reduction in dopaminergic medication doses, and the hypothesis of changes in neuronal firing in basal ganglia, with downstream effects on the thalamus and diencephalospinal dopaminergic pathway leading to an improvement of RLS, was raised [13,14].

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We aimed to specifically identify factors associated with the risk of developing RLS after DBS-STN in order to enhance our comprehension of the underlying mechanisms contributing to the occurrence of RLS in PD.

## 2. Methods

In this study, we prospectively assessed the occurrence and severity of RLS, both preoperatively and postoperatively at six months, in 35 consecutive patients with PD who underwent DBS-STN at Clermont-Ferrand University Hospital from March 2008 to September 2012. All the patients met the requirements of the United Kingdom Parkinson Disease Society Brain Bank criteria [15]. They all suffered from severe motor fluctuations and LIDs that were not improved by changes in their antiparkinsonian treatment. The selection criteria for DBS-STN were: an excellent response to Levodopa tested during an acute Levodopa challenge (>50%), no postural instability during the best on period (postural instability = 0) from item 29 of the Unified Parkinson's Disease Rating Scale (UPDRS Part III) [16], absence of dementia (Mini Mental Status > 24) [17], and normal brain magnetic resonance imaging. The surgical procedure was based on the direct location of STN using stereotactic nuclear magnetic resonance (NMR) and electrophysiological mapping (recording and stimulation of the STN area) as reported elsewhere [18]. Four of the 35 patients submitted to DBS-STN reported RLS symptoms preoperatively and they were therefore excluded, in order to specifically investigate risk factors associated with the emergence of RLS after DBS-STN. Thus, this study included 31 patients who were free from RLS symptoms preoperatively. We compared the group of patients with a postoperative emergence of RLS (RLS+) with the group of patients without postoperative emergence of RLS (RLS–) for clinical and demographical features, dopaminergic treatment and stimulation parameters.

All patients gave their informed consent for participation. The protocol was approved by the local ethical board (2013/CE61).

### 2.1. Design of the study

PD patients were evaluated for parkinsonian symptoms, treatment and presence and severity of RLS symptoms one month before surgery (preoperatively), and 6 months after surgery (postoperatively) by a neurologist expert in movement disorders and in sleep disorders.

### 2.2. Parkinsonian symptoms assessment

Parkinsonian symptoms were assessed using the unified Parkinson's disease rating scale (UPDRS) [16]. One month before surgery, response to Levodopa was evaluated using UPDRS Part III in the 'Off' state after 12-h withdrawal of antiparkinsonian medication, and in the 'On' state after taking 1.5-times the usual morning Levodopa dose using dispersible Levodopa (Modopar Dispersible, Roche).

Six months after surgery, the acute efficacy of DBS-STN and of Levodopa was assessed in the morning after at least 12 h of withdrawal of antiparkinsonian medication using UPDRS Part III in four conditions: 'medication off – stimulation off', 'medication off – stimulation on', 'medication on – stimulation on', 'medication on – stimulation off'. The medication condition was tested with the same dose and galenic form as preoperatively. For DBS investigation, 'stimulation off' meant that stimulation had been switched off for at least 1 h, and 'stimulation on' meant that stimulation had been switched on for at least 1 h.

The chronic effect of DBS-STN was also assessed with the items 32 (duration of dyskinesia), 33 (incapacity linked with dyskinesia) and 39 (duration of the off periods) of UPDRS Part IV, and with the Hoehn and Yahr scale [19].

### 2.3. Treatment doses and stimulation parameters

The doses of antiparkinsonian drugs were recorded before surgery and at 6 months of follow-up, and were expressed as LEDD [20]. Thus, when assessing treatment doses we considered the following parameters: total treatment (encompassing all antiparkinsonian drugs), DA (dopamine agonists only), and non-DA (all antiparkinsonian drugs excluding dopamine agonists). We noted absolute values of treatment at pre- and postoperative evaluations, but also the mean percentage change. The following stimulation parameters were noted bilaterally: voltage (V), pulse width (μs), and frequency (Hz).

### 2.4. RLS assessment

During the preoperative and postoperative visit, PD patients were questioned about the presence of RLS according to the IRLSSG criteria [21], namely: (1) an urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; (2) symptoms begin or worsen during periods of rest or inactivity such as lying or sitting; (3) symptoms are partially or totally relieved by movement, such as walking or stretching; (4) symptoms occur or worsen in the evening or night. RLS diagnosis was made when all the four criteria were met. When RLS was found, its severity and frequency were rated using IRLSSG rating scale [22]. RLS assessment was conducted when patients were under their usual treatment and stimulation 'on'.

### 2.5. Statistics

Considering this work as an exploratory study, a posteriori estimation of statistical power was proposed. Statistical analyses were performed using Stata software, version 12 (StataCorp, College Station, TX, USA). The tests were two-sided, with a type I error set at $\alpha = 0.05$. Baseline and post-operative characteristics were presented as the mean ± standard deviation (SD) or median (interquartile range, IQR) for each group (RLS+ and RLS–) for continuous data, and as the number of patients and associated percentages for categorical parameters. These parameters were compared between groups using the Chi-squared or Fisher's exact test for categorical variables, and Student's *t*-test or Mann–Whitney test for quantitative variables, with normality verified by the Shapiro–Wilk test and homoscedasticity by the Fisher–Snedecor test. Due to sample size, non-parametric tests were often preferred. Considering the sample size and univariate results, no multivariate analysis was considered. We chose to report all the individual *p*-values without carrying out any mathematical correction for distinct tests comparing two groups [23]. Particular focus was given to the magnitude and clinical relevance of the results [24].

## 3. Results

Demographical and clinical data, as well as dopaminergic treatment of the whole sample, are shown in Tables 1 and 2. Stimulation parameters related to DBS-STN are shown in Table 3.

Median preoperative improvement in the UPDRS-III score after levodopa was 73.33% [63.16; 81.82]. DBS-STN induced an improvement of the UPDRS III score and of the motor complications subscores (items 32, 33 and 39 of the UPDRS-IV) of 44.26% [53.16; 29.69] and of 61.90% [75.00; 33.33] respectively at six months. At six months, total treatment was reduced by 33.33% [60.42; 9.30] and DA by 33.33% [100.00; 0.00] in our sample.

Six patients out of 31 (19%) reported postoperative onset of RLS. For these patients, the median severity score of RLS symptoms on the International Restless Legs Syndrome Study Group (IRLSSG) rating scale was 16 [14; 19]. The IRLSSG rating scale indicated severe (21–30) RLS in only one of these patients, and moderate (11–20) in five.