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Different outcomes for dyskinesia and off-period dystonia after deep brain stimulation for Parkinson's disease—Review and a new hypothesis

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ABSTRACT

In this review analyzed are the results of several clinical studies that addressed effects of deep brain stimulation (DBS) on motor complications of levodopa therapy, with emphasis on off-period dystonia. All studies found significant decrease in UPDRS IV scores (dyskinesia and motor fluctuations), regardless of target (STN or GPi), for up to 11 years after the surgery. Data from the studies show that the benefit of DBS for dyskinesia lasts longer than for off-period dystonia. Motor scores deteriorate to baseline after approximately 3 years of stimulation, while dyskinesia continue to benefit up to 11 years after surgery (longest follow-up). Interestingly, dyskinesia often resolve regardless of whether active stimulation is present, while off-dystonia always requires active stimulation. DBS works better for phasic (mobile) then tonic type of dystonia (such as off-dystonia). The effect of DBS on off-period dystonia is best within 1–2 years after the surgery and declines thereafter, tending to follow deterioration of motor scores. Only one study reported on effectiveness of GPi DBS for off-period dystonia, with resolution after one year and no further follow up. Further comparative studies are needed to provide evidence which target is better suited for patients with off-dystonia (and wearing-off) and whether targeting GPi provides a comparable benefit, or more. For this purpose, better and unified scaling system is needed for quantifying off-period dystonia in PD. Considerations in this paper lead to discussions presented in Appendix, where there is also presented a fundamental issue of obsolete D2 receptor activation during levodopa therapy and the need for metoclopramide in preventing wearing-off/off-dystonia.

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1. Introduction

There is a high prevalence of dystonia in patients with idiopathic Parkinson's disease (PD) [1,2]. Dystonia can be a manifestation of underlying PD or may be related to levodopa therapy. Up to 60% of patients with onset of PD before 40 years of age have co-existent dystonia [3]. Dystonic movements and postures increase in frequency and severity with longer duration of levodopa treatment [4]. To which extent this is the result of natural history of the disease or L-DOPA related remains largely not understood. PD-related dystonia often starts in the toes or foot and on the side with initial or most severe parkinsonian signs [5].

Levodopa is believed to have a variable effect on dystonia in patients with PD—it may improve dystonia or exacerbate it. The mechanism for this is unknown until present and will be discussed in the Appendix section.

Levodopa-related dystonia most commonly presents as "wearing off" or "off-period" dystonia—usually early morning dystonia with low plasma DOPA levels. It is usually painful, rather exasperating and disabling feature of advanced Parkinson's disease. More rarely it appears as biphasic dystonia associated with short-duration levodopa response and often strong psychological component, or "peak-dose" dystonia with high plasma DOPA levels [5,6]. Neurosurgical approaches that have been used in the treatment of PD and dystonia include stereotactic pallidotomy, thalamotomy and deep-brain stimulation (DBS).

It is generally accepted that stimulation of GPi is preferred treatment for patients with primary dystonia, although some recent studies have reported benefit with STN DBS [7]. Conversely, STN stimulation is favored more for patients with Parkinson's disease, but this preference is also put into question [31]. Both STN and GPi DBS are considered to be effective treatments for motor fluctuations and dyskinesia associated with PD. However, it is less clear how effective DBS is for off-period dystonia and how long after the surgery the benefit remains satisfactory.

In this review we analyzed the results of several clinical studies that addressed DBS effects on motor complications of levodopa therapy in PD, with emphasis on off-period dystonia.

2. Methods

The literature search was performed using Pubmed from 1960 to March 2016 using the following terms: deep brain stimulation, Parkinson's, off-period dystonia, STN, GPi, dyskinesia, UPDRS IV and motor complications/fluctuations. Bilateral STN and unilateral or bilateral GPi stimulation were considered. The task was somewhat hindered by the fact that in their studies authors used different methodology and scoring systems. Some studies employed overall UPDRS IV score, at baseline and follow-up, others employed UPDRS IV part A and part B, some further separated between UPDRS items or used different dyskinesia scoring. Some studies compared outcomes between DBS and best medical therapy (BMT), others between STN and GPi DBS. Follow-ups varied between 3 months and 11 years. We compiled a total of one class I, nine class III evidence studies that estimated UPDRS IV scores (dyskinesia and motor fluctuations) before and after DBS surgery and four class IV evidence studies that distinctively focused on off-period dystonia pre- and postoperatively. Only 1 study was classified as class I, as it included sham-operated control patients who received an electrode in the STN which was not activated until 3 months after the surgery (19). Class III studies were all randomized with exception of one study. The conceivable absence of controls has artificially downgraded some class III studies.

3. Results

3.1. Dyskinesia and motor fluctuations (UPDRS-IV)

All studies found significant decrease in UPDRS IV scores after the surgery. Compared with best medical therapy, DBS was much better in reducing the scores. Dyskinesia and motor fluctuations score (UPDRS IV A and B) improvement was similar regardless of target (STN or GPi) [11,18,21]. Tendency for UPDRS IV scores was to remain stable at subsequent follow-ups, although slight increase was usually evident after 5 years or later (Table 1).

Interestingly, one study [8] shows further improvement in UPDRS IV A (dyskinesia duration and disability) after each follow up at 1, 5 and 10 years after the surgery. Likewise, Simonin et al. show further improvement of dyskinesia, but not of off-dystonia, at 5 years compared to 1 year of follow-up [9].

Anderson et al., 2005 show that dyskinesia score was stably reduced one year after the surgery, regardless of whether stimulation was present or not. However, at 3 months after the surgery active stimulation was still required for that effect [11]. Pibulnoorak et al. show that mean daily dyskinesia duration decreases from 1.7 h to 0.4 h, 3 years after the surgery [12].

3.2. Adverse dyskinesia

New onset, DBS related (adverse) dyskinesia varied between studies (1–25%). It developed commonly after increase in voltage within first 3 months, but improved later [13].

3.3. Off-period dystonia

In the study of 49 patients with STN stimulation, 71% of patients had painful off-dystonia before surgery, which decreased to 19% at one year and increased to 33%, five years after the surgery, on stimulation [13].

Four class IV studies specifically estimated off-period dystonia after DBS surgery (Table 2). Off-dystonia, commonly manifested as early morning dystonia, improved significantly with GPi stimulation, although only one study reported on this [14]. Authors tried to better define off-period dystonia and developed a scale that assesses dystonia in six different parts of the body (neck, trunk, upper and lower extremities at each side), scoring the severity from 0 to 4, for a total of 24 points. With unilateral GPi DBS, contralateral off-period dystonia improved by 100% at 1 year postoperatively. With bilateral GPi DBS, total scores for off-dystonia improved by 86%. The benefit appeared early, at first follow up 3–5 days after the surgery and was stable after one year. Authors also found similar decrease in dystonia-associated pain, cramps and dysaesthesia. STN stimulation also ameliorated off-period dystonia [8,9,13,15]. Simonin et al. used CAPSIT-PD scale to assess off-dystonia and on-dyskinesia in 33 patients with STN DBS. They found improvement of dyskinesia one year after the surgery, which further improved after five years of stimulation, often regardless of whether stimulation was acutely on or off. Levodopa was also less able to induce dyskinesia during acute dopaminergic challenge, after 5 years of DBS. They found less robust, although still significant, resolution of off-dystonia after years 1 and 5. Unlike dyskinesia, off dystonia was significantly better only when stimulation was on [9]. One study showed improvement of off dystonia (UPDRS-IV C) only during first year and return to baseline after 5 and 10 years of STN-DBS [8].

3.4. Medications adjustment and stimulation parameters

LED (levodopa equivalent daily dose) was significantly reduced after the surgery in STN, but not in GPi group. However, in a