Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait

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Bilateral subthalamic nucleus (STN) stimulation improves the gait and freezing items on the Unified PD Rating scale (UPDRS) to a similar extent as L-dopa.\(^1\) The time needed to perform the stand-walk-sit test is also reduced.\(^1\) Bilateral surgery or stimulation of either the internal pallidum (GPI) or the STN is required to improve axial symptoms such as the gait disorder in patients with PD.\(^2,3\) A quantitative study investigating the effects of STN stimulation on gait in patients with PD is lacking so far.

After several years of treatment, freezing of gait may become resistant to L-dopa.\(^4\) It has not been assessed whether L-dopa-resistant freezing may respond to STN stimulation. Because it has been proposed that preoperative L-dopa-resistant freezing predicts the clinical outcome after STN stimulation,\(^3\) our interest was focused on patients who exhibited a gait disturbance with severe freezing even in their best "on" condition before surgery.

**Patients and methods.** Nine patients with PD (mean age, 56 ± 7 years; Hoehn and Yahr score, III to V) were studied 3 months after bilateral electrode implantation in the STN for deep brain stimulation (DBS). Seven patients had an L-dopa-responsive gait disorder (Group 1) and two patients were identified preoperatively as having severe freezing episodes, even at their best L-dopa response (Group 2). Ten age-matched, healthy subjects served as controls.

Before gait analysis on a treadmill, the natural walking speed of each patient was measured during overground locomotion in each of the four conditions. Subsequently, a complete gait analysis was carried out on a treadmill, with the speed adjusted exactly to the subjects' individual gait velocities as measured before. Gait was recorded with a three-dimensional infrared movement analysis system, comprising four infrared cameras and video processors (50-Hz sampling rate) connected to a computer. Different gait measurements, including kinematics, were calculated using self-developed software.\(^5\)

**Results.** After surgery, the UPDRS motor score was reduced by 45% with stimulation in the off-drug condition (Group 1, figure 1A). The gait score improved by 58% (see figure 1B). In the patients with “on”-period freezing, the UPDRS motor score was improved to a similar extent as in Group 1 (see figure 1A), whereas the gait score remained much higher, mainly due to persisting freezing episodes (see figure 1B).

Compared with the control subjects, gait velocity and stride length were significantly lower in the patients with PD in all conditions (figure 2). The cadence was only slightly reduced. The coefficient of variation of the stride length was high (42%) in the off-stimulation, off-drug condition compared with control subjects (3%). The step height was lower in patients with PD during the off-stimulation, off-drug condition (79 ± 39 mm) than in control subjects (180 ± 15 mm). The range of the joint motions was reduced in patients with PD in the hip (3°), the knee (24°) and the ankle (11°) compared with the control subjects (hip, 24°; knee, 52°; and ankle, 18°).

With DBS, the stride length increased massively (see figures 2 and 3A). Compared with the off-drug, off-stimulation condition, the gait velocity increased by 184% with DBS, comparable to the effect of L-dopa (+193%). Both treatments together further increased gait velocity by approximately 30%. The increase in gait velocity was mainly caused by an increase of stride length, which was more important with L-dopa (+148%) than with stimulation (+124%). The coefficient of variation of the strides decreased from 42% to 8% with stimulation. The cadence, which was 99 steps/minute in the off-drug, off-stimulation condition, increased with L-dopa (to 108 steps/minute) and
was normalized by stimulation (119 steps/minute vs 120 steps/minute in control subjects). The height of steps was raised with stimulation (+80%), L-dopa (+91%), and both (+108%), ameliorating the shuffling gait pattern. The range of motion was increased with STN stimulation in the hip (from 3° to 18°), knee (24° to 39°), and ankle (11° to 18°). L-Dopa treatment also increased range of motion in the hip (from 3° to 24°), knee (24° to 40°), and ankle (11° to 21°).

Freezing of gait occurred in all patients in the “total off” condition and was totally relieved by DBS or L-dopa treatment in all patients of Group 1. Postoperatively freezing and therefore gait was not much improved in the patients with “on”-condition freezing (Group 2) (see figure 1B). There was an additional effect on gait when stimulation and L-dopa were combined, even in the patients with “on”-period freezing.

Discussion. This is the first study investigating the impact of bilateral STN stimulation on gait using formal gait analysis. There was a considerable improvement of gait due to an increase in gait velocity, stride length, cadence, and gait kinematics. Stimulation had more effect on cadence and L-dopa had more effect on stride length.

Stride length regulation is believed to be controlled in the basal ganglia, whereas cadence generation might be under the control of the locomotor regions at midbrain or spinal level. These different mechanisms may be responsible for the differential effects of L-dopa and STN stimulation. Both treatments were complementary and their combination resulted in a further increase of gait velocity. One patient with “on”-period freezing had a clear-cut, long-lasting benefit when both stimulation and medication were combined, whereas a reduction of either stimulation or medication led to an immediate worsening of gait.

Gait is improved to a greater extent by bilateral STN stimulation than bilateral GPi surgery. Can possible differences in the effect on gait between STN stimulation and GPi surgery be explained from

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**Figure 1.** (A) Individual Unified PD Rating Scale (UPDRS) motor scores (with mean and SD) on and off L-dopa treatment before and after bilateral subthalamic nucleus (STN) stimulation (stim) in patients with PD with an L-dopa–sensitive gait disorder (full circles, solid line) and two patients with “on”-period freezing (open circles, dashed line). (B) UPDRS gait score (with mean and SD) on and off L-dopa treatment before and after bilateral STN stimulation in patients with PD with an L-dopa-sensitive gait disorder (full circles, solid line) and patients with “on”-period freezing (open circles, dashed line).

**Figure 2.** Gait velocity (A), stride length (B), and cadence (C) in control subjects and patients with PD (Group 1) under four different conditions of stimulation and medication. Control subjects are represented by open bars. The off-stimulation, off-drug condition is represented by black bars; on stimulation, off drug by light gray bars; off stimulation, on drug by dark gray bars; and on stimulation, on drug by striped bars. The * symbol indicates a significant difference (p < 0.05) between control subjects and patients with PD; # indicates a significant difference (p < 0.05) between on stimulation, off drug and off stimulation, off drug; and * indicates a difference (p < 0.05) between on stimulation, off drug and on stimulation, on drug.
the pathophysiologic point of view? In addition to the loss of nigral dopaminergic cells, patients with PD have a marked cell loss in the pedunculopontine nucleus (PPN),9 which is part of the mesencephalic locomotor region. Bilateral lesions of the PPN in monkeys induced an akinetic syndrome, which was pronounced in proximal muscles.7 The PPN receives γ-aminobutyric acid (GABA)-ergic inhibitory input from the GPi and the substantia nigra. Both the GPi and substantia nigra receive excessive excitatory glutamatergic input from the STN in parkinsonism. A blockade of the STN by DBS would thus result in a disinhibition of PPN neuronal activity via both the GPi and substantia nigra, whereas GPi stimulation would only influence one of these pathways.

The pathophysiology of freezing is poorly understood, but a dysfunction or a disconnection of the basal ganglia and the frontal lobes has been assumed to cause this peculiar phenomenon.10 “Off”-period freezing is mostly sensitive to L-dopa and responded excellently to DBS in our study. In patients with advanced PD, however, freezing may become resistant to dopaminergic medication. The change in response to L-dopa during the course of the disease may reflect increasing involvement of nondopaminergic systems, such as cholinergic cell loss in the PPN.9 If this holds true, neither L-dopa nor STN stimulation would be expected to improve “on”-period freezing. Our data indeed suggest that “on”-period freezing is not a good indication for bilateral STN stimulation. Our findings again validate the principle that only those symptoms that have been shown to improve with L-dopa or dopamine agonists will respond to STN stimulation.4

References

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