Effect of bilateral subthalamic nucleus stimulation on parkinsonian gait

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Abstract Clinical reports show that bilateral subthalamic nucleus (STN) stimulation is effective in improving parkinsonian gait. Quantitative analysis of the efficacy of STN stimulation on gait is of interest and can be carried out using a commercially available stride analyser. Ten parkinsonian patients (5 men, 5 women) with a mean age of 55.8, SD 9.6 years were included in our study. They had a mean duration of Parkinson's disease (PD) of 13.3, SD 4.5 years and a motor examination score (part III of the Unified Parkinson's Disease Rating Scale) (UPDRS) of 43, SD 13 in off-stimulation off-drug condition. All the patients had bilateral chronic STN stimulation which had started from 3 to 36 months before the study. Patients were evaluated in off-drug and on-drug conditions both with and without stimulation. We analysed the principal gait measures : velocity, cadence, stride length, gait cycle, duration of single and double limb support. The clinical parkinsonian signs were evaluated with the part III of the UPDRS. In the off-drug condition, STN stimulation significantly ($p < 0.05$) improved velocity and stride length. The effect was similar to that of levodopa. When STN stimulation was switched on at the best of the levodopa induced effect, no further improvement was observed. The UPDRS motor score was significantly ($p < 0.001$) decreased after both stimulation and levodopa. In conclusion, STN stimulation is effective on parkinsonian gait.

Key words Parkinson's disease · Gait · Subthalamic nucleus · Deep brain stimulation

Introduction

Gait disturbances are one of the major symptoms of Parkinson's Disease (PD). Typical parkinsonian gait includes short shuffling steps and slow walking velocity with decreased amplitude of the segmental movements. Gait impairment is frequent in the advanced stages of PD, can induce falls and severe disability in activities of daily living. Treatment of this disorder is important in order to give patients physical and psychological support. Therefore, quantitative analysis of the effect of a new treatment on gait is particularly interesting. The beneficial effect of levodopatherapy on some gait parameters has been widely reported [2, 7–8, 14, 16, 19, 23, 34, 37]. The fundamental problem in gait disturbance of PD is regulation of stride length [31]. Levodopa increases stride length and velocity (kinematic parameters), while temporal parameters related to rhythm are levodopa resistant [7].

Since 1993, clinical reports have shown that subthalamic nucleus (STN) stimulation can greatly alleviate the main motor signs and symptoms of PD, including gait [25–27, 29–30]. Yokoyama et al. [38] focused on the pos-

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itive effect of unilateral STN stimulation on gait in 5 parkinsonian patients assessed by a subjective method. Bejjani et al. [3] found that bilateral STN stimulation improved most axial features of PD (including gait) and that a synergistic effect could be obtained when stimulation is used in conjunction with levodopa treatment. An objective analysis of the effect of STN stimulation on parkinsonian gait has not yet been published. Thalamic stimulation did not change parkinsonian gait studied by an opto-electronic system [10]. We studied the effect of both levodopa and STN stimulation on gait parameters using a commercially available stride analyser.

Materials and methods

Patients

Ten patients (5 men, 5 women) with idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [17] were included in our study. All the patients had bilateral chronic STN stimulation (DBS 3389 electrode, Medtronic, Minneapolis, MN, USA). Electrode implantations were carried out according to a procedure already described [27]. These patients were consecutively chosen on the occasion of a follow up of their STN stimulation in our hospital. Table 1 summarizes the patients' characteristics. Four patients had mild off-drug dystonia of the lower limbs without stimulation and 8 patients had dyskinesia in on-drug period with and without stimulation. Patients were excluded where cardiovascular, musculoskeletal, psychiatric or visual disturbances could influence walking. No patients were demented (score on the Mini Mental State Examination ≥ 24/30) [15]. They were able to walk 8 meters at least 4 times with only stand-by supervision in off-motor condition (off medication and off stimulation).

All patients gave their informed consent for this study.

Methods

Gait analysis was carried out using a commercially available stride analyser (B and L Engineering, Santa Fe Springs, California, USA) that is widely used to assess gait parameters in PD [31–32]. This system consisted of a pair of foot switches, a manual start-stop controller and a recorder for data storage. The foot switches in the shape of thin insoles were put in the subject's shoes and contained 4 sensors to detect the floor contact for the heel, first metatarsal, fifth metatarsal and big toe. An open time on the foot switches when the foot contacted the floor and an off time when the foot left the floor were calculated. The start-stop controller was triggered by the investigator pushing a button at the beginning and end of an 8-meter walkway. The recorder, worn on a waist-belt, collected data for each trial within a maximal time of 131 seconds. The acquired data was transferred from the recorder to PC for storage and analysis. The application software used for the analysis was the 'Stride Analyzer' version 2.4 (B & L Engineering, 1995). This device could quantitatively analyse the following gait measures: velocity (m/min), cadence (steps/min), stride length (m), gait cycle (GC) (seconds), swing and stance phases (% GC), single (seconds) and double (% GC) limb support. A cream colour linoleum of 10 meters length was put on the floor to obtain a neutral walkway and a movable door frame of 70 cm width might be put in the middle of the walkway in order to increase the difficulty of passage. A video-camera was also used for this study to control the clinical correlation with the stride analyser data if necessary, after the experiment.

For all therapeutic conditions, the PD patients performed four gait trials, firstly two without the movable door frame and secondly two with. A two-minute rest was taken between each trial. Two trials before recording were carried out to familiarize patients with the testing conditions. The instruction to the patients was: 'walk at your normal speed to the end of the walkway'. Patients were studied firstly in off-drug condition (i. e. after an overnight fasting of at least 12 hours without PD medications), on and off stimulation and secondly in on-drug condition (i. e. at least 40 minutes after the oral intake of a suprathreshold levodopa dose), (mean dose [SD] of levodopa: 189, 65 mg) [12], on and off stimulation. The order of the two stimulation conditions was randomized, with a 10-minute latency between each change of stimulation condition. A double-blind design was not possible because both the patients and the examiner became aware of the condition of stimulation given the dramatic and almost immediate effect of STN stimulation on parkinsonian features. The stimulation parameters were those normally used, with a mean (SD) frequency of 144 (20) Hz (range: 130–185 Hz), a constant pulse width of 60 µs, a mean (SD) voltage of 2.8 (0.7) V (range: 1.4–3.6 V) and a monopolar cathodic current using one contact of the quadripolar electrode. The motor examination in the four conditions was evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) part III [13]. In addition, two trials of a stand-walk-sit test [9] were performed in the four

Table 1 Clinical characteristics of the studied PD patients

No.	Age (years)	Sex	Height (cm)	Weight (kg)	Lower limb length (cm)	Disease duration (years)	Levodopa duration (years)	Stimulation duration (months)	Hoehn & Yahr stage (off/on)[1]	Levodopa dose (mg/day)[2]	Dopamine agonist dose (mg/day)[3]
1	50	M	178	85	104	12	12	24	3/2	950	B 15
2	44	M	166	62	103	8	4	6	3/2	400	B 15
3	68	M	170	72	102	10	10	6	2.5/2.5	825	B 15
4	58	M	178	90	104	18	18	36	3/2.5	1000	0
5	39	F	160	68	97	9	5	6	3/3	500	B 7.5
6	53	F	160	46	97	18	18	3	2.5/2.5	475	0
7	64	F	164	65	98	16	16	12	2.5/2.5	375	B 25
8	64	F	170	63	101	7	7	3	3/3	625	B 15
9	64	F	160	57	96	18	16	3	3/3	350	B 15
10	54	M	168	63	100	17	16	3	2.5/1.5	400	B 30
Mean	55.8	5M	167.4	67.1	100.2	13.3	12.2	6 (median)	2.8/2.5	590	
SD	9.6	5F	6.8	12.8	3.0	4.5	5.4	3–36 (range)	0.3/0.5	247	

[1] Hoehn & Yahr stage was evaluated in on stimulation condition

[2] 100 mg of controlled-release levodopa = 75 mg of standard levodopa, the total dose is expressed as the standard levodopa equivalents

[3] B = Bromocriptine

conditions. We also studied the two lower limb movement time in four patients. These patients were asked to touch two points on the floor, 30 cm apart, 10 times with the big toe of each foot, in a sitting position.

The mean values of the different gait parameters, UPDRS subscores and timed tests in the four conditions were used for comparison. The analysis of statistical differences of gait parameters, UPDRS subscores and timed tests among the four conditons in PD patients was made by the Kruskal-Wallis test. Then, if this test showed significant differences, a Wilcoxon signed rank paired statistical test was performed to compare two conditions. The comparison between the two conditions, with and without door frame, was made by the Wilcoxon signed rank paired statistical test.

Results

Clinical data

Table 2 shows the results of the UPDRS part III scores, duration of the stand-walk-sit test and duration of the movement test in the lower limbs in the four conditions. Levodopa and STN stimulation significantly improved the score of the UPDRS part III ($p < 0.001$) and the duration of the stand-walk-sit test ($p < 0.05$), but stimulation did not induce any further benefit in on-drug condition. The percentages of STN stimulation-induced improvement were 56 % for the score of the UPDRS part III and 32 % for the duration of the stand-walk-sit test. In four patients who performed the movement timed test in the lower limbs, the execution time decreased after both STN stimulation and levodopa. No statistical test was carried out because of the small number of patients.

Table 2 Clinical results in PD patients in the four experimental conditions

Clinical evaluation	Off medication		On medication	
	Off Stim	On Stim	Off Stim	On Stim
UPDRS III Mean score (SD) N=10	43 (13)	19 (10)	19 (14)	13 (9)
Mean duration of stand-walk-sit test (SD) (sec) N=10	31 (19)	21 (10)	17 (5)	16 (5)
Median duration of movement test in LL R/L (sec) N=4	11/12	10/11	9/9	8/8

Stim: stimulation; LL: lower limbs; R/L: right/left

Gait analysis

The results of different gait parameters are shown in Table 3. PD patients had a slower velocity and shorter stride length. The velocity and stride length were significantly ($p < 0.05$) improved by both STN stimulation and levodopa to the same magnitude. The double limb support duration was shorter but not significantly ($p=0.06$). The percentages of improvement by STN stimulation were 41 % for the velocity and 33 % for the stride length. Switching the stimulation on in the on-drug condition did not improve the gait parameters further. The cadence, gait cycle and duration of single limb support were not significantly changed in the four test conditions. There was no significant difference between the walking conditions with and without the door frame in the four conditions.

Discussion

Our results show that the walking pattern of parkinsonian patients is characterized by slowness and short steps. The obstacle (door frame) did not significantly change the gait measures. This can be explained by the selection of patients able to walk even in off-medication off-stimulation condition, reflecting a moderate severity of gait impairment. However, we expected episodes of freezing of gait, known to be easily triggered by the passage under a door frame [18], whereas no freezing episode was observed, whatever the experimental condition. Since these patients underwent a few episodes of freezing in their everyday lives, the absence of freezing of gait during the study suggests that the experimental test condition induced psychological changes beneficial to freezing of gait. Since disturbances of gait rhythm (e. g. festination or freezing) were not encountered in these patients, our result applies to the hypokinetic/

Table 3 Gait parameters (mean ± SD) obtained with the stride analyzer in PD patients

Parameters	Off medication		On medication	
	Off Stimulation	On Stimulation	Off Stimulation	On Stimulation
Velocity (m/min)	39.7 ± 18.4	55.9 ± 13.5	63.1 ±12.6	64.0 ± 13.3
Cadence (steps/min)	99.4 ± 17.9	105.5 ± 12.0	107.9 ± 12.8	109.9 ± 10.0
Stride length (m)	0.80 ± 0.32	1.06 ± 0.20	1.17 ± 0.20	1.17 ± 0.23
Gait cycle (GC) (sec)	1.25 ± 0.28	1.17 ± 0.14	1.13 ± 0.14	1.10 ± 0.10
Single limb support (sec)				
R	0.37 ± 0.14	0.39 ± 0.07	0.38 ± 0.07	0.37 ± 0.06
L	0.40 ± 0.12	0.39 ± 0.06	0.38 ± 0.09	0.38 ± 0.05
Double limb support (% GC)				
R	39.0 ± 9.9	33.2 ± 4.9	33.8 ± 6.1	32.7 ± 5.4
L	39.3 ± 10.3	33.3 ± 4.9	33.8 ± 6.4	32.5 ± 5.3

bradykinetic aspects of parkinsonian gait. The main result of this study is the similar improvement in gait parameters induced by both levodopa and bilateral STN stimulation. This improvement in gait is in keeping with that of the motor examination score of the UPDRS and the stand-walk-sit test.

Gait disturbance in PD and the effect of levodopa on gait have been widely studied, using different methods. The main impairments of gait features in PD are a slower velocity, a shorter stride length, a tendency to a longer duration of the double limb support[2,6–8, 14, 16, 19, 22–23, 31–34, 36–37], but a cadence within the normal range [31–33, 36]. Our results are similar to these reports. Levodopa intake increases velocity, stride length, and decreases the duration of the double limb support [2, 7–8, 14, 16, 19, 23, 34, 37]. However, after the administration of levodopa, cadence was increased in some reports [19] and not changed in the others [7, 34] as in our study. Chronic bilateral STN stimulation improves akinesia, rigidity and tremor in patients with severe PD [21, 24–27, 29–30]. The exact mechanism of STN stimulation is still unknown. It was suggested that high-frequency stimulation inhibits the STN activity known to be increased in PD [1, 4–5,11]. In our PD patients, the improvement in gait measures was accompanied by a similar improvement in the parkinsonian triad. Therefore, gait improvement by the STN stimulation is related to the decrease in total motor disability, including akinesia and rigidity of the lower limbs. The decrease in movement time of the lower limbs that we found in four of the PD patients who performed this test favours this hypothesis. Thalamic stimulation mainly reduced tremor but did not improve the gait parameters [10]. Procedures that improve akinesia and rigidity can also improve gait, as reported after pallidotomy and mostly bilateral pallidotomy [35]. However, we cannot exclude that STN stimulation influences other neuronal pathways outside the cortex-basal ganglia-thalamus-cortex loop. Among the connections of the STN that are not directly related to dopaminergic pathways, such as the cortex, the parafascicular nucleus of the thalamus and the pedunculopontine nucleus (PPN), only the last receives a direct output from the STN. It has been suggested that the PPN is involved in the relay of information for locomotion. Bejjani et al. [3] showed an improvement of STN stimulation added to that of levodopa. However, this further improvement mainly concerned posture and postural stability, that was minor in comparison to the benefit on akinesia and rigidity.

The mechanism underlying gait disorder in PD is also not clear. Morris et al. [31] have suggested that the fundamental deficit in PD gait is the internal regulation of stride length, because when the stride length was normalized using external cues the other gait parameters were approximately equal to normal values. This might be due to inadequate preparatory processes involving the interaction between the supplementary motor area (SMA) and the basal ganglia. The effect of gait on brain activity was studied in a single photon emission computed tomography. Brain activity was reduced in the medial frontal motor areas, including the SMA, in parkinsonian patients compared with control subjects who showed an increased brain activity in these areas [20]. Another study using positron emission tomography in the PD patients with STN stimulation showed that a movement-related increase in brain activity during effective STN stimulation was higher in SMA, cingulate cortex and dorsolateral prefrontal cortex than during ineffective stimulation [28].

In conclusion, our results showed that STN stimulation is effective on parkinsonian gait and the effect of STN stimulation on gait seems to mimick that induced by levodopa. Since stride length improvement paralleled the improvement in all levodopa responsive symptoms, a normalization of the frontal cortical activity may account for gait improvement induced by both STN stimulation and levodopa.

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