Effect of subthalamic deep brain stimulation on gait in patients with advanced Parkinson's disease

Efecto de la estimulación cerebral profunda subtalámica sobre la marcha en pacientes con enfermedad de Parkinson avanzada

Authors

Lina M. Villegas-Trujillo [1]
Juan F. Mier-García [1]
Juan Camilo Salcedo [1]
Sebastián Ordoñez [1]
María José Uparela [1]
Fernanda Arbeláez [2]
Camilo A. Turriago-Pérez [2]
Lesbby Gómez-Salazar [3]
Óscar A. Escobar-Vidarte [1,3,4]

[1] Universidad del Valle (Colombia)
[2] Clínica Zerenia (Colombia)
[3] Hospital Universitario del Valle (Colombia)
[4] Fundación Valle del Lili (Colombia)

Corresponding author:
Óscar A. Escobar-Vidarte
oscar.escobar@correounivalle.edu.co

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Abstract

Introduction: Advanced Parkinson's disease severely affects gait. According to literature, deep brain stimulation of the subthalamic nucleus has scarce impact on gait in this disease.
Objective: To evaluate and compare gait kinematics and parameters in patients with Advanced Parkinson's disease treated previously with deep brain stimulation of the subthalamic nucleus without anti-Parkinsonian medications, in ON and OFF modes of stimulation.
Methodology: This was a single-group pre-post quasi-experimental study and included 11 patients with idiopathic Advanced Parkinson's disease who were treated with deep brain stimulation of the subthalamic nucleus. Gait kinematic measurements were compared between the ON-OFF conditions within the same patients.
Results: A significantly greater range of joint movement was found in the ON condition vs. OFF condition in the knee (42.64° vs. 38.28°, p=0.04) and the ankle (20.42° vs. 16.58°, p=0.04). In the coronal plane, greater joint movement was found in the trunk (4.0° vs. 3.19°, p=0.05). Gait Deviation Index was significantly higher while in ON condition vs. OFF condition (80.23° vs. 75.15°, p=0.06).
Discussion: Although this study yields data that supports the fact that the deep brain stimulation of the subthalamic nucleus positively affects the gait characteristics studied and presented, there are others that have reported contradictory findings, possibly related to methodological limitations.
Conclusions: Patients presented an improvement in gait kinematics and parameters with the effects of deep brain stimulation of the subthalamic nucleus. Gait Deviation Index was sensitive to changes observed under ON-OFF conditions. Studies with larger number of patients are needed to draw more accurate conclusions.

Keywords

Deep brain stimulation; gait analysis; kinematics; Parkinson's disease.

Resumen

Introducción: La enfermedad de Parkinson avanzada afecta gravemente la marcha. Según la literatura, la estimulación cerebral profunda del núcleo subtalámico tiene escaso impacto en la marcha en esta enfermedad.
Objetivo: Evaluar y comparar la cinemática y los parámetros de la marcha en pacientes con enfermedad de Parkinson avanzada tratados previamente con estimulación cerebral profunda del núcleo subtalámico sin medicación antiparkinsoniana, en los modos de estimulación ON y OFF.
Metodología: Este fue un estudio cuasiexperimental pre-post de un solo grupo que incluyó a 11 pacientes con enfermedad de Parkinson avanzada idiopática tratados con estimulación cerebral profunda del núcleo subtalámico. Se compararon las mediciones de la cinemática de la marcha entre las condiciones ON y OFF en los mismos pacientes.
Resultados: Se observó un rango de movimiento articular significativamente mayor en la condición ON que en la condición OFF en la rodilla (42,64° frente a 38,28°, p = 0,04) y el tobillo (20,42° frente a 16,58°, p = 0,04). En el plano coronal, se observó mayor movimiento articular en el tronco (4,0° vs. 3,19°, p=0,05). El índice de desviación de la marcha fue significativamente mayor en condiciones ON vs. OFF (80,23° vs. 75,15°, p=0,06).
Discusión: Si bien este estudio aporta datos que respaldan que la estimulación cerebral profunda del núcleo subtalámico afecta positivamente las características de la marcha estudiadas y presentadas, otros estudios han reportado hallazgos contradictorios, posiblemente relacionados con limitaciones metodológicas.
Conclusiones: Los pacientes presentaron una mejoría en la cinemática y los parámetros de la marcha con los efectos de la estimulación cerebral profunda del núcleo subtalámico. El índice de desviación de la marcha fue sensible a los cambios observados en condiciones ON-OFF. Se necesitan estudios con un mayor número de pacientes para extraer conclusiones más precisas.

Palabras clave

Análisis de la marcha; cinemática; enfermedad de Parkinson; estimulación cerebral profunda.

Introduction

Gait is a unique motor activity controlled by multiple cortical areas, and subcortical and brainstem nuclei; it is complex as it involves locomotion, balance, the ability to adapt to the environment, the integrity of the nervous and musculoskeletal systems, and cognitive and psychological states. Gait alterations result in falls, disability, loss of independence, and correspondent complications and sequelae (Snijders et al., 2007).

Gait alterations are a common problem in neurodegenerative disorders, being an important cause of morbidity and mortality in people with advanced Parkinson's disease (APD), especially in the stages of late motor complications, when gait is characterized by short step length, hesitance and freezing (Johnsen, 2011; Navratilova et al., 2020). This short step length may lead to an inability to walk long distances and therefore affect quality of life, and frequent falls can lead to lack of confidence or injuries (Walkowski et al., 2024).

Deep brain stimulation (DBS) is the surgical procedure most frequently performed for the treatment of APD refractory to medical management; and the subthalamic nucleus (STN) is one of its main targets (Deuschl et al., 2022).

A natural diminishment in the response to and efficacy of Parkinson's disease (PD) pharmacological treatment is a common phenomenon recognized with the progression of this disorder, with a contrasting increase in gait alterations (Zanardi et al., 2021). On the grounds of our clinical observations and documentation, and the evidence of some records previously published (Ferrarin et al., 2005; Johnsen, 2011; Lubik et al., 2006), STN-DBS is as a potential treatment strategy to counteract gait abnormalities in APD, resulting in an increase in its speed and stride length, as well as in the range of motion of the lower limbs joints after surgery (Hariz & Blomstedt, 2022). However, their results in this field are still controversial. For example, in some patients gait difficulties are a consequence of non-dopaminergic symptoms and therefore do not respond to DBS and likewise, depending on the location and quality of surgery, the effects of DBS may vary from one subject to another (Hariz & Blomstedt, 2022). Likewise, given that even after DBS surgery, antiparkinsonian drugs continue to be administered, it is complex to determine how much of the changes in gait can be attributable to the drugs or the stimulator.

The use of objectively assess gait in APD has increased exponentially in the last twenty years (Mollinedo Cardalda et al., 2023; Pereira-Pedro et al., 2023), allowing a comprehensive and computerized analysis for patient evaluation and subsequent therapeutic definitions (di Biase et al., 2020). This type of analysis allows the evaluation of kinematic changes, such as variations in stride length, changes in cadence, gait speed, joint range of motion, among other parameters. Likewise, as a multivariate measure based on 15 gait characteristics from three-dimensional (3D) kinematic data, it is possible to establish the Gait Deviation Index (GDI), whose use in Parkinson's patients is controversial (Galli et al., 2012) has been reported by some authors as sensitive to changes generated by drugs or deep stimulation in Parkinson's patients (Speciali et al., 2014).

In relation to patients with APD treated with DBS, studies have shown that it is possible to analyze different clinical scenarios in which a subject may be on antiparkinsonian medication (ON) or off (OFF), or in other cases, whit their stimulator in active (ON) or inactive (OFF) mode, allowing for the objective determination of the effects of a given intervention. However, few studies have independently evaluated the effects of DBS activation or deactivation without considering the influence of Parkinson's medication.

Considering the prevalence of APD and its potential limiting repercussions for an adequate gait function, our observation and clinical experience, the controversial impact of the STN-DBS on it, and the scarce evidence of correspondent objective evaluations that shed light regarding its impact on gait in our national-regional context (Luna et al., 2018; Rueda-Acevedo et al., 2014; Speciali et al. 2014), this topic becomes relevant; therefore, the objective of this work was to evaluate and compare gait lineal and angular kinematics variables in patients with APD treated previously with STN-DBS without anti-Parkinsonian medications, in ON (case) and OFF (control) modes of stimulation.

Method

The study employed a single-group pre-post quasi-experimental design to evaluate the effects of subthalamic nucleus deep brain stimulation (STN-DBS) on gait in patients with APD. The analysis compared gait laboratory measurements in the same patients under two different conditions: ON-stimulation and OFF-stimulation, always in the OFF-medication state. The research protocol of this study was reviewed, accepted, and endorsed by the Human Ethics Committee of the Universidad del Valle. All the participants signed an informed consent.

Population

Adult patients with idiopathic APD of at least five years of duration, classified as stage IV on the Hoehn-Yahr scale (Severely disabling disease; still able to walk or stand unassisted) (Hoehn & Yahr, 1967), who had previously undergone bilateral electrode implantation for STN-DBS (using Medtronic, Boston Scientific, and Abbott technologies) in the sensory-motor region of the STN in the last three years with the standard stereotactic technique for micro-recording, intraoperative tests, and final placement of electrodes and pulse generators, previously described in the literature by other authors (Anidi et al., 2018). Participants were selected using a random sequence generation method from patients who underwent STN-DBS in one rehabilitation institution.

Patients with extra targets different from the STN, bedridden because of their APD or without significant gait impairment (Hoehn-Yahr stages I, II, III and V), and with limitations or sequelae of the locomotor apparatus potentially conditioning unexpected gait alterations solely explained by the APD were excluded.

Following the application of inclusion and exclusion criteria, 11 patients were included in the final analysis. The sample size was determined based on previous studies assessing gait outcomes following STN-DBS, considering expected effect sizes for key gait parameters. Given the paired nature of the design, where each patient served as their own control, a sample of 11 was estimated to provide sufficient statistical power to detect moderate-to-large effect sizes in gait improvement, assuming a power of 80% ($\beta = 0.2$) and a significance level of $p<0.05$.

Experimental protocol

In these patients, a computerized analysis of the gait was performed, without the administration of anti-Parkinsonian medications 12 hours prior to its execution, evaluating the following parameters (Saunders et al., 1953; Schwartz & Rozumalski, 2008):

- Speed: Meters per minute walked.
- Cadence: Number of steps per minute.
- Step length: Distance between heels when taking a step, measured in meters.
- Step width: Linear distance in meters between two equal points of the feet while walking.
- Percentage of support: Duration of the gait cycle phase in which both lower limbs are in contact with the ground, expressed as a percentage.
- Gait Deviation Index (GDI): An indicator of how far the subject's gait deviates from the normal standard, with 100 being a perfect score.
- 3D joint kinematics: Relative movement of the parts of the body during different phases of a walk, with angular maximums and minimums for each joint and the amplitude of the movement.

Gait recordings were performed in ON and OFF stimulation conditions (the latter after 15 minutes of turning off the device's pulse generator). For each condition, subjects performed eight walking tests at their preferred speed along a 10-meters track.

Gait tests for the evaluation of spatial and temporal variables were performed with Vicon Nexus 2.12.1 and Vicon Polygon 4.4.6 technologies (Vicon Motion Systems, Oxford, Oxfordshire, Englanda) using eight Vicon MX T40, infrared cameras, and two digital video Bonita cameras from Vicon. In addition, a set of

10 mm reflective markers were positioned following the conventional gait model established in the Davis protocol (Davis et al., 1991) (Figure 1). This protocol has been used widely in the APD research (di Biase et al., 2020; Russo et al., 2025; Tramontano et al., 2016). The equipment used was calibrated before each test according to factory protocols and has been validated useful in gait analyses in healthy people and people with APD (Luna et al., 2018; Speciali et al., 2014).

Figure 1. Gait laboratory

The experimental protocol was carried out at the gait laboratory at the Clínica Zerenia. The results were interpreted by an orthopedist (CATP) and a physiotherapist (FA), experts in computerized gait analysis

Statistical analysis

The normality of each result was verified with the Shapiro-Wilk test for the choice of a given analysis, using parametric or non-parametric tests. The results were then evaluated using repeated measures analysis of variance. For data that did not comply with normality, the median, and interquartile range were reported, and the differences between scores in ON-OFF stimulation conditions of the gait analysis variables were analyzed using the Wilcoxon paired pair test (Wt).

For the variables that met normality, the mean and standard deviation were reported and the difference between the variables in the two conditions was analyzed with the paired "Student's t" test since the measurements corresponded to the same subject in two different conditions (ON-OFF). The same tests were used for the comparison of the kinematic parameters of the gait. The level of statistical significance was $p<0.05$. Data analysis was performed using the statistical program SPSS v. 25.0.

Results

Eight men and three women, with a mean age of 63±12.72 years were selected for the study. The mean duration of their disease prior to performing the STN-DBS (MDD) and the implantation time at the time of the gait analysis were 8±1.41 years and 16±8.85 months respectively. All the stimulation parameters were conventional (Vítečková et al., 2020). The mentioned variables, and the anti-Parkinsonian medications received with their levodopa equivalent doses (LED) are comprehensively presented in Table 1.

Table 1. Demographic and clinical characteristics of the patients studied.

Patient	Age (years)	Sex (F/M)	MDD (years)	IT (month)	PT	LED (mg)	STN-DBS	
							Right	Left
1	67	M	10	22	LCE, A, P	1648	3.1 V, 62 µs, 106 Hz	2,7 V, 62 µs, 106 Hz
2	63	M	8	30	LC	1500	3.2 V, 60 µs, 150 Hz	4.0 V, 60 µs, 150 Hz

3	66	F	15	36	LC, P	775	4.0 mA, 10 µs, 66 Hz	2.8 mA, 10 µs, 66 Hz
4	47	M	10	10	LB, A	800	3,9 mA, 60 µs, 132 Hz	3.4 mA, 60 µs, 32 Hz
5	65	M	9	28	LC, P	1950	3.8 V, 60 µs, 185 Hz	3.8 V, 60 µs, 185 Hz
6	67	M	8	20	LCE	1330	2.6 mA, 60 µs, 85 Hz	2.5 mA, 50 µs, 85 Hz
7	72	F	10	34	LC	1500	3.2 V, 60 µs, 60 Hz	3.9 V, 60 µs, 60 Hz
8	69	M	11	22	LC, P	1050	2.5 mA, 60 µs, 90Hz	2.4 mA, 60 µs, 90 Hz
9	72	M	7	13	LB, R	1100	4.3 V, 60 µs, 195 Hz	2,0 V, 60 µs, 195 Hz
10	54	M	9	10	LC, P	1400	2,6 V, 60 µs, 120 Hz	2,7 V, 60 µs, 120 Hz
11	59	F	5	19	LCE, P	1400	2.5 mA, 60 µs, 90Hz	2.6 mA, 60 µs, 90 Hz

MDD: Evolution time of the disease at the time of implantation. F: female. M: Masculine. IT: Implantation time at the time of the gait analysis. PT: Pharmacological treatment. LED: Levodopa equivalent daily dose. STN-DBS: Stimulation parameters and active pole or poles for stimulation. LC: levodopa/carbidopa. LB: levodopa/benserazide. LCE: levodopa/carbidopa/entacapone. A: Amantadine. Q: Pramipexole. R: Rasagiline. SD: Standard deviation. STN-R: Right subthalamus. STN-L: Left subthalamus. V: volts. mA: Milliamps. µs: Microseconds. Hz: Hertz

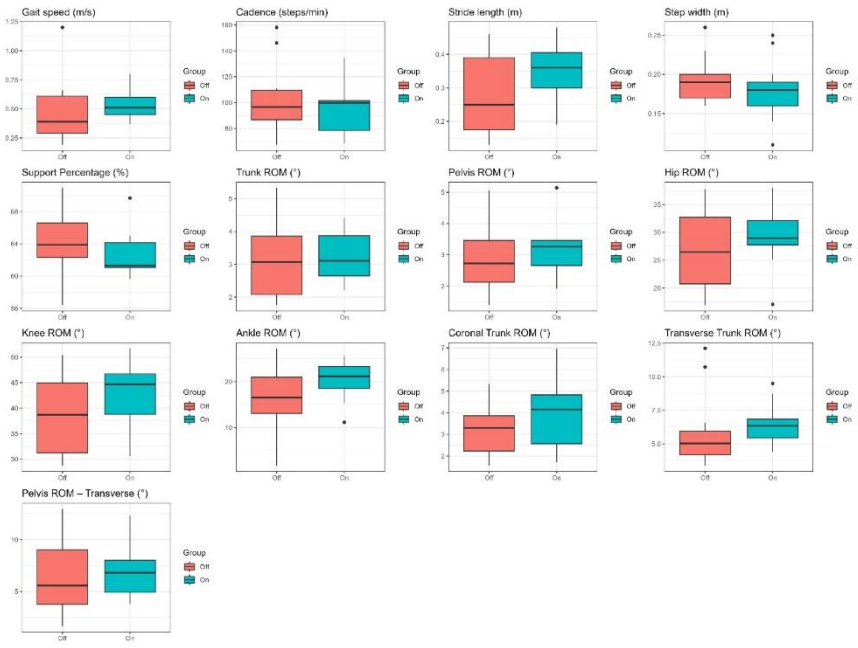
Patients with APD had a higher speed, lower cadence, greater stride length, and lower support percentage in the ON condition; however, the differences were not statistically significant for this group of spatial and temporal variables (Table 2, Figure 2).

Table 2. Comparison of spatial and temporal gait parameters during OFF and ON conditions.

Gait Parameters	OFF*	ON*	Difference ON-OFF*	Effect size (dz)**	P value
Gait speed (m/s) [a]	0.48 [0.29, 0.67]	0.54 [0.45, 0.63]	0.06 [-0.15, 0.27]	0.18	0.56
Cadence (steps/min)	102.34 [83.1, 121.58]	93.61 [80.61, 106.62]	-8.73 [-23.39, 5.94]	-0.40	0.21
Stride length (m)	0.28 [0.2, 0.37]	0.35 [0.29, 0.41]	0.07 [-0.01, 0.15]	0.60	0.07
Step width (m)	0.19 [0.17, 0.21]	0.18 [0.15, 0.21]	-0.01 [-0.03, 0]	-0.51	0.12
Support Percentage (%) [a]	64.31 [61.67, 66.96]	62.71 [60.78, 64.63]	-1.61 [-4.86, 1.65]	-0.33	0.3

*Off and On columns represent the mean and 95% confidence interval (CI), calculated using a t-distribution.
**Effect size (dz)" indicates Cohen's dz for paired samples, which quantifies the magnitude of the effect.
Superscript (a): Median (interquartile range).
SD: standard deviation.

Figure 2. Comparison of spatial, temporal and kinematics gait parameters during OFF and ON conditions.



Fuente: Elaboración propia de los autores.

The GDI index reported in the OFF condition of the patients was on average 75.15, while in the ON condition it increased to an average of 80.23, however, it did not represent a statistically significant difference (p=0.06) (Table 3, Figure 2). Regarding gait kinematics, a greater range of joint movement was found in the ON condition compared to the OFF condition in the knee (42.64 versus 38.28 degrees, p=0.04) and the ankle (20.42 versus 16.58 degrees, p=0.04) with statistical significance. In the coronal plane, greater joint movement was found in the trunk in the ON condition (4.0 versus 3.19 degrees, p=0.05). In the transverse plane there were no statistically significant differences in the variables analyzed (Table 3).

Table 3. Comparison of gait kinematics during the STN-DBS: OFF, STN-DBS: ON conditions.

Gait kinematics	OFF*	ON*	Difference ON-OFF*	Effect size (dz)**	P value
		Sagittal			
Trunk ROM (°)	3.09 [2.32, 3.87]	3.26 [2.74, 3.79]	0.17 [-0.41, 0.75]	0.20	0.53
Pelvis ROM (°)	2.86 [2.15, 3.57]	3.13 [2.56, 3.7]	0.27 [-0.5, 1.05]	0.24	0.45
Hip ROM (°)	27.1 [22.1, 32.09]	29.24 [25.47, 33]	2.14 [-1.94, 6.23]	0.35	0.27
Knee ROM (°)	38.28 [33.01, 43.54]	42.64 [38.39, 46.9]	4.37 [0.37, 8.36]	0.73	0.04
Ankle ROM (°)	16.58 [11.65, 21.51]	20.42 [17.49, 23.35]	3.85 [0.3, 7.39]	0.73	0.04
		Coronal			
Trunk ROM (°)	3.19 [2.35, 4.03]	4 [2.86, 5.13]	0.8 [-0.01, 1.62]	0.66	0.05
		Transverse			
Trunk ROM (°) [a]	5.91 [3.99, 7.84]	6.43 [5.4, 7.46]	0.52 [-0.68, 1.71]	0.29	0.36
Pelvis ROM (°)	6.36 [3.96, 8.77]	6.85 [5.07, 8.62]	0.48 [-0.8, 1.76]	0.25	0.42
		GDI			
Average GDI [a]	75.15 [68.75, 81.56]	80.23 [75.14, 85.31]	5.07 [-0.14, 10.29]	0.65	0.06

*Off and On columns represent the mean and 95% confidence interval (CI), calculated using a t-distribution.
**Effect size (dz)" indicates Cohen's dz for paired samples, which quantifies the magnitude of the effect.
ROM: joint range of motion in degrees (°), superscript (a): Median (interquartile range). GDI: Gait Deviation Index. NA: Not applicable. SD: Standard deviation

Discussion

The results of our study differ from other published works evaluating the effect of bilateral STN-DBS on gait in patients with APD with the use of a computerized analysis (Gavriliuc et al., 2020; Navratilova et al., 2020; Rizzone et al., 2017; Seger et al., 2021).

Patients' demographics, technologies used for DBS, MDD, LED and time without anti-Parkinsonian medications are comparable to previously published data (Gavriliuc et al., 2020; Rizzone et al., 2017; Seger et al., 2021; Speciali et al., 2014; Zanardi et al., 2021). An average implantation time of 16 ± 8.42 months corresponds to a strength of this study, being considered as acceptable for a sufficient adaptation to the functional changes product of a STN-DBS (Navratilova et al., 2020).

Concerning the waiting time between turning off the pulse generators and the corresponding evaluation of the OFF state at the gait laboratory, there is no consistent definition in the literature in this regard (Allert et al., 2001; Anidi et al., 2018; Navratilova et al., 2020), so 15 minutes were considered as an adequate time for the individual subjective recovery and subsequent performance of the designated tasks.

Adequate and precise gait analysis in patients with APD that undergo any treatment is crucial to evaluate the efficacy of said treatment and if necessary, establish specific modifications to the therapeutic method in order to contribute to the well-being and quality of life of these patients (Bella et al., 2017; Gaßner et al., 2022). Our measurements and analysis of gait parametric and kinematic variables in an OFF-medication condition, discriminating the performance of patients in ON vs. OFF stimulation modes suggest an increase in gait speed, stride length, and range of joint mobility, with a consequent decrease in cadence and percentage of support; and despite not having achieved statistical significance in some variables, our findings suggest that STN-DBS might have a positive impact on gait, being these variables of value in the functionality and mobility of patients (Peterson et al., 2020; Zanardi et al., 2021).

Zanardi et al. (2021) in a recent systematic review and meta-analysis included studies comparing the analysis of spatiotemporal variables and angles of the lower limbs during gait in patients with APD without DBS in relation to healthy subjects. The authors found a lower gait speed (0.17 m/s) in patients with

APD compared to the healthy participants, which is comparable to the gait speed gain in the ON condition found in our study (0.06 m/s). Likewise, we found similar results in the stride length, step width and percentage support prolongation parameters. On the other hand, we found greater cadence in the ON condition (8.73 steps/min) compared to the results reported by Zanardi et al. (2021) where the cadence found in patients with APD was only 1.75 steps /min higher than in the healthy subjects. Regarding kinematics, we found similar results to Zanardi et al. (2021) in terms of sagittal range of motion of the hip. However, while in their study the sagittal range of motion of the knee and the ankle remained unchanged in patients with APD vs. healthy participants, we did find statistically significant average ON-OFF gain in those variables.

Similarly, Gougeon et al. (2017) characterized the trunk mobility ranges in the different planes in patients with APD without DBS. The impact of the STN-DBS in each of them is also presented according to our measurements: 4.51° in the sagittal (average ON-OFF gain: 0.17° in this work); 8° in the coronal (average ON-OFF gain: 0.8° in this work); and 4.58° in the transverse plane (average ON-OFF gain: 0.52° in this work). And although the gains found in these variables were modest compared to others, different studies relate less trunk mobility to postural instability and a greater risk of falls, and this beneficial effect of the STN-DBS may contribute to mitigating both situations (Peterson et al., 2020).

With scarce previous records by Speciali et al. (2014), Galli et al. (2012) and Pinto de Souza et al. (2017) addressing partially this topic, this is the first study to describe a comprehensive GDI analysis in patients with APD and STN-DBS, a measure that fully integrates all the kinematic variables studied, with average improvement of 6.16 points in an ON stimulation condition with statistical significance and clinical relevance, meaning a gait closer to normal parameters when patients experience the beneficial effects of STN-DBS.

Although there are meta-analyses and other studies reporting some biomechanical parameters of gait in patients with APD and STN-DBS, they do so in a marginal and tangential ways, without a precise description of the measurement methods used (Gavriliuc et al., 2020; Navratilova et al., 2020; Seger et al., 2021; Vítečková et al., 2020; Zanardi et al., 2021).

The relevance of our findings is supported by the methodological approach used, as we decided not to rely on less detailed questionnaire scales of gait functionality, prospectively acquiring and using a complete gait laboratory, with real-time monitoring, and computerized information processing, measuring quantified and specific parameters in the form of figures and tables, corresponding this to an objective and accurate strategy for estimating the impact of the effect of the STN-DBS on gait. An accurate evaluation of this effect is important to reach a comprehensive evaluation of the patient and to define the most adequate therapeutic approach.

Although our study yields data that supports the fact that the STN-DBS positively affects the gait characteristics studied and presented, there are some others that have reported controversial or contradictory findings, possibly related to the methodological limitations of the evaluation of gait variables with different stimulation targets other to the STN (Collomb-Clerc & Welter, 2015; Pötter-Nerger & Volkmann, 2013; Zanardi et al., 2021).

Limitations

The main limitation of our study is the small sample size. Studies including larger number of patients are necessary to be able to analyze with greater statistical power gait spatial, temporal, and kinematic parameters, determining its precise response to STN-DBS in patients with APD. Moreover, we acknowledge that gait examination under laboratory conditions cannot account for external influences seen in a real environment such as walking down a busy street, the need to go around furniture or poor visibility. Therefore, our results should be interpreted with caution.

Conclusions

According to our results, patients with APD can show an improvement in the spatial, temporal, and kinematic parameters of gait with the effects of STN-DBS. The impact seen on the GDI suggests a function closer to a normal gait in severely ill patients. Studies with a larger number of patients are needed to analyze the compared variables with greater statistical power.

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Authors' and translators' details:

Lina M. Villegas-Trujillo	lina.villegas@correounivalle.edu.co	Author
Juan F. Mier-García	juan.mier@correounivalle.edu.co	Author
Juan Camilo Salcedo	juan.salcedo@correounivalle.edu.co	Author
Sebastián Ordoñez	sebastian.ordonez@correounivalle.edu.co	Author
María José Uparela	maria.uparela@correounivalle.edu.co	Author
Fernanda Arbeláez	fernanda_arbelaez@hotmail.com	Author
Camilo A. Turriago-Pérez	caturriago@gmail.com	Author
Lesbby Gómez-Salazar	lessby.gomez@correounivalle.edu.co	Author
Óscar A. Escobar-Vidarte	oscar.escobar@correounivalle.edu.co	Author
Juan F. Mier-García	juan.mier@correounivalle.edu.co	Translator