Title: Subthalamic Nucleus Deep Brain Stimulation in Early-Onset Parkinson's Disease: Clinical Outcomes in LRRK2 Mutation Carriers Compared to Non-Carriers

Running Title: STN-DBS in Early PD: LRRK2 vs Non-LRRK2

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Abstract:

Introduction: Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) is an established treatment for early-onset Parkinson's disease (EOPD). While the effect of STN-DBS on patients with LRRK2-G2019S mutation has been largely investigated, data specific to EOPD patients with this mutation remain scarce. This study assesses how the G2019S mutation impacts STN-DBS outcomes in EOPD patients in Morocco, a developing country where such treatment is challenging to provide.

Methods: A prospective cohort study was conducted at the University Hospital of Ibn Rochd in Casablanca. Genomic DNA was analyzed for LRRK2-G2019S mutation, and clinical data were collected pre- and post-surgery. Motor outcomes, including dyskinesia, motor fluctuations, and levodopa equivalent daily dose (LEDD) reduction, were assessed one-year post-DBS.

Results: Seventeen EOPD patients who underwent STN-DBS were included, with 10 (58.8%) being LRRK2-G2019S mutation carriers. The mean age of participants was 57.2 ± 8.4 years, with an average age at onset of 37.9 ± 6.2 years. Motor fluctuations were present in 88.2% of patients, and 94.1% experienced dyskinesia. Post-DBS, both mutation carriers and non-carriers showed significant improvements in motor symptoms, with a mean UPDRS III improvement of 61.3%. Dyskinesia and motor fluctuations, as measured by specific UPDRS IV items, improved by 77.1% and 83.8%, respectively, with a mean LEDD reduction of 60.6%. Improvements were comparable between G2019S carriers and non-carriers. All patients were satisfied with the treatment, though one patient had a hardware-related infection.

Conclusion: STN-DBS is effective in managing motor symptoms and reducing medication needs in EOPD patients, regardless of LRRK2-G2019S mutation status.

Keywords: Early-onset Parkinson's disease, Deep brain stimulation, Subthalamic nucleus, LRRK2 mutations.

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that predominantly affects individuals in their 60s, with prevalence increasing with age, impacting 1% to 2% of those over 65 (Ascherio & Schwarzschild, 2016; Van Den Eeden et al., 2003). Early-onset Parkinson's disease (EOPD) has been variably defined, with the maximal age ranging from 40 to 60 years, until expert consensus in 2022 set the threshold at motor symptom onset before 50 (Mehanna et al., 2022), accounts for approximately 3% to 7% of PD cases (Mehanna & Jankovic, 2019). Genetic factors are strongly associated with EOPD, with the likelihood of detecting genetic mutations increasing as the age of onset decreases (Blauwendraat et al., 2020). In North Africa, specific mutations, such as the LRRK2 G2019S, are prevalent among PD patients (El Otmani et al., 2023), although their precise relation with EOPD has not been thoroughly investigated.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a well-established treatment for managing motor and non-motor complications and reducing the need for dopaminergic medication in PD advance stages (Deuschl et al., 2006). Emerging evidence supports its efficacy in EOPD (Krause et al., 2022), who often experience earlier motor complications and lower overall quality of life compared to late-onset PD patients (Knipe et al., 2011; Kumar et al., 2005). While STN-DBS appears particularly effective in LRRK2-PD patients (Leaver et al., 2022), data specifically focusing on EOPD patients with these mutations remain limited, with no previous studies investigating this relationship.

This study aims to fill this gap by exploring the impact of LRRK2 G2019S mutation on the clinical outcomes of EOPD patients undergoing STN-DBS, where resources in a developing country like Morocco add complexity.

Patients and Methods

Study design and population

This prospective study was conducted at the University Hospital of Ibn Rochd in Casablanca, Morocco. The study included patients diagnosed with EOPD, defined in our cohort as disease onset at age 45 or younger -a threshold established prior to the 2022 consensus, which later set the cutoff at motor symptom onset before age 50- who underwent STN-DBS between June 2007 and June 2023. Participants were selected according to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria (Hughes et al., 1992). Eligibility for DBS was determined based on the CAPSIT-PD criteria (Defer et al., 1999), which included: an acute levodopa challenge test demonstrating improvement greater than 50% in motor symptoms measured by the UPDRS III, a neuropsychological assessment with a Moroccan version of the Mattis scale exceeding a score of 140, a favorable psychiatric status evaluated preoperatively by a psychiatrist to rule out contraindication (with depression assessed using the MADRS scale), and preoperative MRI findings showing no substantial atrophy, signal abnormalities, or structural lesions. All patients provided informed consent prior to inclusion in the study, and the research was approved by the local ethics committee.

Genomic DNA was extracted from saliva samples using the Oragene-DNA kit. Genotyping for LRRK2 mutations was performed using TaqMan SNP Genotyping Assays, with PCR and real-time detection. Based on genetic results, patients were divided into two groups: those who tested positive for LRRK2 G2019S mutation (carriers) and those who did not (non-carriers). The non-carriers did not have any known monogenic mutations, including PARKIN, PINK1, DJ-1, or GBA.

Surgical procedure

A stereotactic neurosurgical implantation of leads into the STN was performed under local anesthesia. Precise coordinates for targeting the dorsolateral part of the STN were calculated using 1.5-T brain MRI. During the procedure, three recording microelectrodes were inserted, and neuronal activity was recorded starting from 10 mm above the target. After placing the DBS leads, we assessed the effect of the stimulation current while the patient was awake, monitoring for motor improvements and side effects. Postoperative CT scans were conducted to identify complications. Pulse generators were implanted on the same day or shortly thereafter, and programming of the DBS device began 2 to 4 weeks post-surgery, with adjustments made during follow-up visits.

Data collection and statistical analysis

We collected demographic and clinical data for all patients. Motor symptoms were evaluated before surgery and reassessed one year post-surgery. A genetic study was conducted alongside the surgical procedure, with some analyses completed up to 18 months ago. To ensure a standardized evaluation of post-surgical outcomes, we established a one-year follow-up period. The primary outcome measures included improvements in motor function, evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III during OFF periods, and reduction in dyskinesia and motor fluctuations based on specific UPDRS IV items. Additionally, decrease in the levodopa equivalent daily dose (LEDD) were calculated using the conversion formulae proposed by (Tomlinson et al., 2010). Improvements were quantified by calculating the percentage change between pre- and post-surgery scores, calculated by subtracting the initial value from the final value, dividing the result by the initial value, and multiplying by 100. Any complications related to DBS surgery or device implantation were also recorded.

Data were analyzed using IBM SPSS Statistics 21. Descriptive statistics were used to summarize demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. Depending on the distribution, comparisons between LRRK2 mutation carriers and non-carriers were performed using t-tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data. For categorical variables, chi-square tests were used, or Fisher's exact tests when expected counts were low. A p-value of <0.05 was considered statistically significant.

Results

Sociodemographic and clinical characteristics

Seventeen EOPD patients who underwent STN-DBS were included, selected from a cohort of 62 PD patients operated on at our center. Of these, 10 (58.8%) carried LRRK2 G2019S mutation. The mean age at disease onset was 37.9 years, and the majority of the sample were females (64.7%). The mean age at surgery was 49.6 years, with an average disease duration of 11.7 years. In terms of clinical presentation, motor fluctuations were present in 88.2% of the patients, and dyskinesia affected 94.1%. The akinetic-rigid PD subtype was the most common (47.1%), followed by mixed type (41.2%) and tremor-dominant type (11.8%). The mean daily dosage of levodopa was 894 mg. All patients were on dopa therapy, 16 out of 17 were on dopamine agonists, 5 were on trihexyphenidyl, and 12 used amantadine. Nearly one-quarter of the patients (23.5%) were on antidepressants. Table 1 provides details of the demographic and clinical characteristics of the sample.

When comparing carriers and non-carriers, G2019S patients were more likely to present with the mixed PD subtype, while non-carriers were predominantly affected by the akinetic-rigid or

tremor-dominant subtypes (p = 0.011). No other significant differences were found in the demographic or clinical characteristics between the two groups as shown in Table 1.

Stimulation settings

We used three stereotactic trajectories (central, internal, and posterior) for all patients to measure electrophysiological activity. The central trajectory was selected for 7 of 10 mutation carriers and 5 of 7 non-carriers, as it provided the longest neuronal recording and the most significant improvement. Regarding DBS settings, in the LRRK2 group, 15 leads were used in monopolar stimulation and 5 in bipolar stimulation, with an average voltage of 2.3V (range: 1.7–2.9) at one year. Among the non-carriers, 11 leads were used in monopolar stimulation and 3 in bipolar stimulation, with an average voltage of 2.4V (range: 1.4–3.2) at one year.

Clinical outcomes at one-year post-DBS

After one year of STN-DBS, both LRRK2 G2019S mutation carriers and non-carriers demonstrated significant improvements in motor symptoms, with no significant difference between LRRK2 carriers and non-carriers. The mean UPDRS III improvement was 61.3% for the overall cohort. Improvements in dyskinesia and motor fluctuations were also comparable between the two groups, with an overall improvement of 77.1% and 83.8%, respectively. The reduction in LEDD was also notable. The overall cohort achieved a mean reduction of 60.6%. Table 2 provides an overview of these improvements observed in both patient groups.

All patients reported improvements in their quality of life and expressed satisfaction with the treatment outcomes. One patient experienced a hardware-related infection 18 months post-surgery, necessitating device replacement a year later. No other significant complications were reported in the cohort.

Discussion

This study demonstrates that STN-DBS is an effective intervention for managing motor symptoms and reducing medication needs in EOPD patients. However, our findings indicate that the LRRK2 G2019S mutation does not alter DBS outcomes, with no significant difference observed in motor function ($p = 0.922$), dyskinesias ($p = 0.454$), fluctuations ($p = 0.158$), or LEDD reduction ($p = 0.580$) when comparing carriers to non-carriers at one year after DBS. Our series is the first to examine the effect of DBS specifically on EOPD linked to the LRRK2 G2019S mutation. While previous studies (Leaver et al., 2022; Perju-Dumbrava et al., 2012; Sayad et al., 2016) have compared DBS outcomes in LRRK2-associated PD, they focused on all PD patients and did not specifically target EOPD. Moreover, performing such advanced procedures in Morocco, a developing country with healthcare challenges, including workforce shortages and limited access to DBS specialists (Daghi et al., 2024a), is a significant accomplishment.

Both LRRK2 mutation carriers and non-carriers showed significant improvements in motor function, which is consistent with previous reports on DBS efficacy in EOPD (Krause et al., 2022). A review of twelve studies comparing DBS responses across various forms of PD, including carriers of LRRK2, PRKN, and GBA mutations, found that DBS effectively controls motor symptoms regardless of the genetic status of patients or age at onset (Rizzone et al., 2019). While these studies confirmed the overall effectiveness of DBS, they also noted some differences in the response to DBS based on genetic factors. However, the very long-term effects of DBS remain uncertain among EOPD patients carrying the mutations.

While LRRK2 mutations are the most common genetic cause of familial and sporadic PD in our region (El Otmani et al., 2023), it is still unclear whether this translates into differential DBS eligibility. In one study, patients with EOPD carrying LRRK2, GBA or PRKN mutations

were more frequently found in the DBS group compared to the non-DBS group (26.5% vs. 16.8%; P = 0.02) (Pal et al., 2016), suggesting a potential link between these mutations and eligibility for DBS. Our results align with this, as the prevalence of LRRK2 mutations in our group was approximately 58%, notably higher than the 41% previously reported among PD patients in our country or any other prevalence reported globally (Bouhouche et al., 2017; El Otmani et al., 2023). As well, the higher prevalence of LRRK2 mutations in our DBS group (58%) compared to the 5.1% reported in a previous study (Pal et al., 2016) confirms regional genetic differences, possibly driven by a founder effect in this area (El Otmani et al., 2023).

Approximately two-thirds of our DBS patients were female (64.7%), with a higher prevalence reported among LRRK2 group (80%). A previous meta-analysis investigating gender differences in LRRK2-associated PD confirms this findings (Chen et al., 2020). This may be due to earlier onset and faster progression in LRRK2-PD females, with evidence showing a 5-year earlier onset in this subgroup (Trinh et al., 2014). However, other studies have found no significant gender differences in LRRK2 mutation prevalence (Gan-Or et al., 2015).

Multiple studies have shown that patients with younger age at disease onset tend to exhibit better-long term outcomes, particularly in motor and axial symptoms (Shalash et al., 2014). In our study, STN-DBS led to significant improvements, with dyskinesia reduced by 77.1% and motor fluctuations by 83.8%. These results surpass the 66.7% and 50% reductions reported in a previous local study and exceed outcomes from other STN-DBS studies across the African region (Daghi et al., 2024b). Additionally, the reduction in LEDD in our cohort was 60.6%, slightly higher than the 51.72% reduction reported in a previous study from Rabat (Rahmani et al., 2018). All our patients reported satisfaction with the treatment, with only one patient experiencing an infection. These favorable outcomes are likely linked to the younger age at surgery (mean 49.6 years), as younger patients generally respond better to DBS, compared to older ages reported in Rabat and other studies (Daghi et al., 2024b; Rahmani et al., 2018).

There are several limitations to this study. The sample size was relatively small, and the cohort was monocentric, which restricts the generalizability of our findings. Additionally, since the last surgical interventions and genetic studies were conducted up to 18 months ago, the follow-up period was limited to one-year post-surgery. As a result, this timeframe may not adequately capture the long-term durability of DBS effects in EOPD patients. Future studies with larger, multicenter cohorts and longer follow-up periods are needed to confirm these results and to assess the long-term durability of DBS in this patient population. Moreover, while we did not evaluate other variants associated with EOPD, such as PARKIN or GBA, their potential influence on DBS outcomes warrants further exploration.

Conclusion

In conclusion, STN-DBS effectively manages motor complications and reduces medication needs in EOPD, irrespective of whether patients carry the LRRK2 G2019S mutation. At one year post-surgery, our patients experienced a 61.3% improvement in motor function, with dyskinesia and motor fluctuations reduced by 77.1% and 83.8%, respectively, and daily medication doses reduced by 60.6%.

Ethics Statement: The patients were fully informed about this research and gave consent to its publication.

Conflicts of Interest: The authors have no potential conflicts of interest to disclose.

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Tables/Figure Legends

Table 1. This table presents the demographic and clinical characteristics of participants stratified by LRRK2 carrier status. Variables are expressed as mean ± standard deviation for continuous data and as number (percentage) for categorical data. Statistical comparisons between LRRK2 carriers and non-carriers were conducted using Mann-Whitney U, chi-square, or Fisher's exact tests, as appropriate.

Table 2. This table summarizes the clinical outcomes of early-onset Parkinson's disease patients with and without LRRK2 mutations one year after undergoing deep brain stimulation. Results are presented as mean ± SD, with comparisons conducted using t-tests or Mann-Whitney U tests as appropriate.

Table 1. Demographic and clinical characteristics of the participants, mean ± SD or N (%).

	Overall	LRRK2	Non-LRRK2	p-value
Demographics				
Age, years	57.2 ± 8.4	58.2 ± 8.4	55.9 ± 8.7	0.807
Sex, male	6 (35.3)	2 (20)	4 (57.1)	0.115
Family history				
familial	9 (52.9)	7 (70)	2 (28.6)	0.059
sporadic	8 (47.1)	3 (30)	5 (71.4)	
Clinical characteristics				
Age at onset, years	37.9 ± 6.2	37.2 ± 4.8	38.9 ± 8.1	0.520
Age at DBS, years	49.6 ± 6.6	48.8 ± 5.5	50.7 ± 8.1	0.624
Disease duration, years	11.7 ± 1.2	11.6 ± 1.3	11.9 ± 1.2	0.800
PD subtype				
akinetic-rigid type	8 (47.1)	3 (30)	5 (71.4)	0.010
mixed type	7 (41.2)	7 (70)	0 (0)	
tremor-dominant type	2 (11.8)	0 (0)	2 (28.6)	
Daily dosage of levodopa, mg	894 ± 422	896 ± 380	891 ± 507	0.601
Motor fluctuations	15 (88.2)	9 (90)	6 (85.7)	0.585
Dyskinesia	16 (94.1)	10 (100)	6 (85.7)	0.218

* Mann-Whitney U, chi-square or Fisher's exact test, as appropriate. Abbreviations: DBS = Deep Brain Stimulation; LRRK2 = leucine-rich repeat kinase 2; PD = Parkinson's disease.

Legends. This table presents the demographic and clinical characteristics of participants stratified by LRRK2 carrier status. Variables are expressed as mean ± standard deviation for continuous data and as number (percentage) for categorical data. Statistical comparisons between LRRK2 carriers and non-carriers were conducted using Mann-Whitney U, chi-square, or Fisher's exact tests, as appropriate.

Table 2. Clinical outcomes of patients with early-onset Parkinson's disease by study groups (LRRK2 carriers vs non-carriers) at one year after DBS, mean ± SD.

	LRRK2 carriers			**Non-carriers**			**Overall improvement**	**p-value***
	Pre-DBS	**Post-DBS**	**Improvement (%)**	**Pre-DBS**	**Post-DBS**	**Improvement (%)**		
UPDRS III (OFF medication)	36.2 ± 11.9	14.3 ± 8.1	60.9 ± 6.2	38.1 ± 12.0	14.0 ± 7.4	61.9 ± 5.3	61.3 ± 5.7	0.922
Dyskinesias (UPDRS IV)	6.1 ± 5.9	1.5 ± 3.0	75.5 ± 9.3	6.0 ± 5.9	1.3 ± 2.5	79.3 ± 8.4	77.1 ± 8.9	0.454
Fluctuations (UPDRS IV)	4.6 ± 2.2	0.85 ± 1.5	81.5 ± 8.8	4.0 ± 2.3	0.7 ± 1.4	87.1 ± 4.9	83.8 ± 7.8	0.158
LEDD	1152 ± 814	474 ± 407	58.5 ± 8.2	1201 ± 814	441 ± 407	63.6 ± 9.9	60.6 ± 8.9	0.580

* The p-value in compares the percentage changes in pre- and post-DBS variables between patients with and without the LRRK2 mutation. A t-test or Mann-Whitney U test was used, as appropriate.

Abbreviations: LEDD = Levodopa Equivalent Daily Dose; UPDRS = Unified Parkinson's Disease Rating Scale.

Legends. This table summarizes the clinical outcomes of early-onset Parkinson's disease patients with and without LRRK2 mutations one year after undergoing deep brain stimulation. Results are presented as mean ± SD, with comparisons conducted using t-tests or Mann-Whitney U tests as appropriate.

Highlights

- STN-DBS is effective in managing motor symptoms in EOPD patients.
- LRRK2 mutations do not significantly affect clinical outcomes post-DBS.
- Dyskinesia and motor fluctuations were reduced in both carriers and non-carriers.
- EOPD patients showed a 61.3% improvement in motor function after one year of DBS.
- Levodopa equivalent daily dose was reduced by 60.6% after DBS.

Plain Language Summary

Parkinson's disease that starts before the age of 50, called early-onset Parkinson's disease (EOPD), can be difficult to manage. In Morocco, doctors studied a treatment called deep brain stimulation (DBS), where electrodes are placed in the brain to help control movement problems. They also looked at whether a genetic change called LRRK2-G2019S affected how well the treatment worked. The study followed 17 EOPD patients at Ibn Rochd University Hospital in Casablanca who underwent DBS. Genomic testing identified 10 (58.8%) as LRRK2-G2019S carriers. Before surgery, most had motor fluctuations (88.2%) and dyskinesia (94.1%)—uncontrolled movements caused by disease or medication. One year after surgery, patients showed major improvements: better movement control, fewer side effects, and lower medication needs. Results were similar whether or not patients had the genetic change. This study shows that DBS can be very effective for people with EOPD, even in places with limited medical resources. It also suggests that having the LRRK2-G2019S mutation does not change how well DBS works, which could help guide treatment decisions in the future.

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