Movement Disorders
CLINICAL PRACTICE
RESEARCH ARTICLE

Leucencephalopathy in Patients with Parkinson's Disease and Deep Brain Stimulation

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ABSTRACT: Background: Leucencephalopathy (LE) is often detected on magnetic resonance imaging in elderly patients. These white matter lesions may interfere with lead trajectories for deep brain stimulation (DBS) in patients with Parkinson's disease (PD) and are associated with complications after DBS surgery.
Objective: This study was conducted to assess the incidence of LE in PD patients and to evaluate correlations with complications after DBS surgery.
Methods: A consecutive cohort of PD patients who underwent DBS surgery in the subthalamic nucleus (STN-DBS) was retrospectively analyzed. The presence and extent of LE were quantified using the Fazekas scale. Postoperative complications were extracted from the medical records. DBS efficacy was calculated using the side-specific motor symptom ratio (Unified Parkinson's Disease Rating Scale, Part III, postoperative stimulation ON/medication *off* divided by preoperative medication *off*) at 1-year follow-up.
Results: A total of 135 PD patients were included in the study. LE was detected in 35.6% (48/135) of the patients. In 87.7% (57/65), LE was mild, in 10.7% (7/65) moderate, and in 1.6% (1/65) severe. A higher incidence of mild to moderate LE did not correlate with postoperative hemorrhage or postoperative infection. There was no correlation of LE with stimulation efficacy ($r = -0.05$, $P = 0.69$) or with surgical index ($r = -0.10$, $P = 0.35$).
Conclusions: Neither was the presence of mild to moderate LE associated with an increased risk for surgical complications, nor did it negatively impact the long-term improvement in motor function after DBS surgery in PD patients. Therefore, mild to moderate LE should not be considered a contraindication for DBS.

In the medical literature, leucencephalopathy (LE) is referred to as white matter changes or white matter hyperintensities, which are often detected on magnetic resonance imaging (MRI) in elderly patients.[1] These lesions are considered a sign of degenerative changes in axons related to demyelination. However, the etiology of LE is heterogeneous and not completely understood. One of the most common risk factors for LE is arterial hypertension-inducing microangiopathy, which manifests as multiple small white matter lesions.[1] An association of Parkinson's disease (PD) with the presence of white matter changes has been reported previously.[2] The prevalence of white matter lesions in patients with PD is between 30% and 50%.[3] Several studies have demonstrated correlations between severe white matter changes and severe motor symptoms in PD patients.[4–8] Furthermore, the volume of white matter lesions in patients with PD is significantly higher than that in elderly patients without PD.[4] Chen et al. found larger hematoma volumes in patients with more severe white matter changes.[9] The presence of white matter changes has also been regarded as a risk factor for intracerebral hemorrhage in elderly patients.[10,11] In 2 previously published studies, white matter changes were reported in almost three-quarters of patients over 65 years who

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Keywords: deep brain stimulation, Parkinson's disease.

Received 17 April 2024; accepted 14 November 2024.
Published online 4 December 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.14294

had an intracerebral hemorrhage.[10,11] However, it remains unclear whether there is a causal relationship between intracerebral hematoma and LE. In particular, the role of LE in patients undergoing surgery for deep brain stimulation (DBS) has yet to be determined. A higher risk for hemorrhage could result in detrimental bleeding complications after surgical procedures for DBS. Additionally, LE may interfere with trajectory planning for the insertion of DBS electrodes and impact the stimulation effect.

In this study, we aimed to assess the incidence of various severity levels of LE in PD patients undergoing DBS surgery and to determine the impact of LE on stimulation efficacy and postoperative complications after DBS surgery.

Patients and Methods

Patient Population

We carried out a retrospective analysis of 135 PD patients, who underwent surgery with implantation of DBS of the subthalamic nucleus (STN) within 6 years (2010–2016). A comprehensive preoperative neurological evaluation was performed, and only patients without contraindications for DBS surgery (ie, after cognitive and standardized levodopa [L-dopa] testing and MRI within 6 months before surgery) were selected to receive DBS-STN. All patients underwent 3 Tesla MRIs under general anesthesia according to a predefined protocol, which included high-resolution contrast-enhanced T1-sequence, T2-sequence, susceptible-weighted imaging, and diffusion tensor imaging. These were used for preoperative trajectory planning.

Imaging Assessment

The preoperative MRI scans were reviewed, and the presence of LE was documented according to the original and modified Fazekas scales by 2 investigators (P.J. and T.G.). These scales are well-established grading systems for evaluating LE, which they define as T2-hyperintense white matter lesions. The original Fazekas scale (according to Franz Fazekas) includes both periventricular lesions of the white matter (0: none, 1: a cap or thin border around the lateral ventricle, 2: thin halo around the lateral ventricle, 3: irregularly formed border of the lateral ventricle reaching into the deep white matter) and separately localized lesions within the deep white matter (0: none, 1: single punctiform lesion, 2: beginning confluence of the single lesions, 3: large merged lesions).[12] The modified Fazekas scale[13] does not divide the lesions into 2 localizations. It focuses on their size (0: none, or little punctiform single lesions [≤9 mm, maximum 3 lesions], 1: focal/ punctiform lesions, single lesion ≤9 mm, grouped lesions <20 mm, 2: beginning confluence of the lesions: single lesion 10–20 mm, grouped lesions >20 mm, maximum bridging between the lesions, 3: merged lesions: single lesions or merged area >20 mm).

Surgery

The surgical procedure for DBS was conducted by 3 experienced neurosurgeons with high expertise in functional neurosurgery. The procedure was performed using the Leksell G frame (Elekta, Stockholm, Sweden). Trajectory planning was performed using the software for stereotactic planning Framelink (Medtronic, Meerbusch, Germany). The surgery was carried out under local or general anesthesia. The impulse generator was implanted usually in the left pectoral region, except if patients had a cardiac pacemaker, in which case the generator was implanted in the right pectoral region.

Outcome Parameters

Motor function was assessed before surgery by a movement disorder specialist using the Unified Parkinson's Disease Rating Scale (UPDRS), Part III. The efficacy of the DBS surgery (the effect of the stimulation) was specified through the surgical index (postop UPDRS-III medication *off*/stimulation ON divided by preOP UPDRS-III medication *off*) at 1-year follow-up. The L-dopa challenge test was conducted as previously described.[14] We also included the documented intraoperative side effects and complications, paying special attention to postoperative bleeding and infections. The surgical index was defined as the quotient of preoperative and postoperative testing (L-dopa challenge test/stimulation test) and is dimensionless. A surgical index of <1 denotes patients in whom the relative reduction in UPDRS-III points upon stimulation exceeds the preoperative L-dopa challenge test.

Additionally, the UPDRS points concerning the axial motor symptoms, including speech, rigidity of the neck, arising from chair, and posture, were separately evaluated. The correlation of axial motor symptoms with the presence of LE was assessed.

Statistical Analysis

Statistical analysis was performed using the GraphPad Prism statistics software (version 9.4.0, San Diego, CA, USA). Descriptive statistics were used to assess patient characteristics. *t*-Test was used to compare mean values between the 2 groups. The correlation coefficient was calculated to evaluate the association between different variables and LE.

Results

Study Population

A total of 135 PD patients who underwent DBS surgery at our center within 6 years (2010–2016) were included in the study. The mean age was 60 ± 7.7 years, 64% (87/135) were men, and 36% (48/135) were women. The mean duration from PD diagnosis to DBS surgery was 10.2 ± 4.5 years. The STN was the chosen DBS target in all patients; 94% (127/135) of patients had surgery under local anesthesia and 6% (8/135) under general anesthesia. The mean number of trajectories used for microelectrode recording (MER) on the left side was 3.6 ± 1.7. The mean

length of the STN signal on the left side was 3 ± 1.2 mm, and the maximum length was 10 mm. The mean number of trajectories for MER on the right side was 3.4 ± 1.8. The mean length of the STN signal on the right side was 3.2 ± 1.3 mm, and the maximum length was 5 mm. A summary of baseline characteristics is presented in Table 1.

Incidence of Leucencephalopathy in the Study Population

According to the modified Fazekas scale, LE was detected in 48% (65/135) of all patients. In 87.7% (57/65) LE was mild, in 10.7% (7/65) moderate, and in 1.6% (1/65) severe (Fig. 1). Periventricular white matter lesions based on the original Fazekas scale were found in 48.1% (77/135) of all patients, whereas 58% (45/77) had mild LE, 38% (29/77) moderate LE, and 4% (3/77) severe LE. Deep white matter lesions based on the original Fazekas scale were seen in 57% (77/135) of all patients, whereas 58.4% (45/77) had mild LE, 37.7% (29/77) moderate LE, and 3.9% (3/77) severe LE. An overview of the incidence of LE according to the original and modified Fazekas scale is presented in Table 2. A higher incidence of LE according to the modified Fazekas scale was associated with higher age ($r = 0.3030$, 95% confidence interval [CI] 0.1412–0.4489, $P = 0.0004$). There were trends toward a higher incidence of LE in men compared to women ($r = 0.1638$, 95% CI −0.005311 to 0.3238, $P = 0.05$), and in patients who had a longer duration of PD ($r = 0.1570$, 95% CI −0.01914 to 0.3237, $P = 0.08$). The mean UPDRS score for axial motor symptoms in the study population without medication was 0.93 ± 0.81 for speech, 2.33 ± 0.85 for rigidity of the neck, 0.74 ± 1.08 for arising from chair, and 1.07 ± 1.06 for posture. The mean overall UPDRS score for axial motor symptoms was slightly higher in the patient group

TABLE 1 *Baseline characteristics of the study population and a comparison of the patient group with and without leucencephalopathy*

Parameters	All	Group with LE	Group without LE	*P*-value
Number of patients	135	48	87	0.0004*
Mean age (SD) in years	59.9 (7.7)	58.3 (7.8)	63.1 (6.5)	
Sex				
Male % (n)	64% (87/135)	75% (36/48)	59% (51/87)	0.05
Female % (n)	36% (48/135)	25% (12/48)	41% (36/87)	
Hoehn & Yahr % (n)				
Stage 1	9% (12/135)	4% (2/48)	12% (10/87)	0.46
Stage 2	25% (33/135)	30% (14/48)	22% (19/87)	
Stage 3	34% (45/135)	34% (16/48)	34% (29/87)	
Stage 4	20% (26/135)	15% (7/48)	22% (19/87)	
Stage 5	12% (16/135)	17% (8/48)	10% (8/87)	
Duration of disease Mean (SD) in years	10.2 (4.5)	11.1 (4.7)	9.6 (4.3)	0.08
Preoperative levodopa test in % Mean (SD)	65.7% (17.9)	61.7% (16.1)	68.5% (18.7)	0.12
Postoperative UPDRS-III stimulation OFF, medication *off* Mean (SD)	42.5 (12.8)	44.5 (12.6)	41.2 (12.9)	0.33
Postoperative UPDRS-III stimulation ON, medication *off* Mean (SD)	16.2 (8.6)	17.5 (7.5)	15.4 (9.2)	0.35
Stimulation efficacy in % Mean (SD)	63.3% (16.1)	62.3% (11.1)	63.9% (18.7)	0.69
Surgical index Mean (SD)	1.02 (0.31)	1.03 (0.39)	1.03 (0.26)	0.95

Abbreviations: SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale; stimulation OFF, without stimulation; medication *off*, without medication for Parkinson's Disease; stimulation ON, with stimulation.

* Represents a significance level of $p < 0.05$.

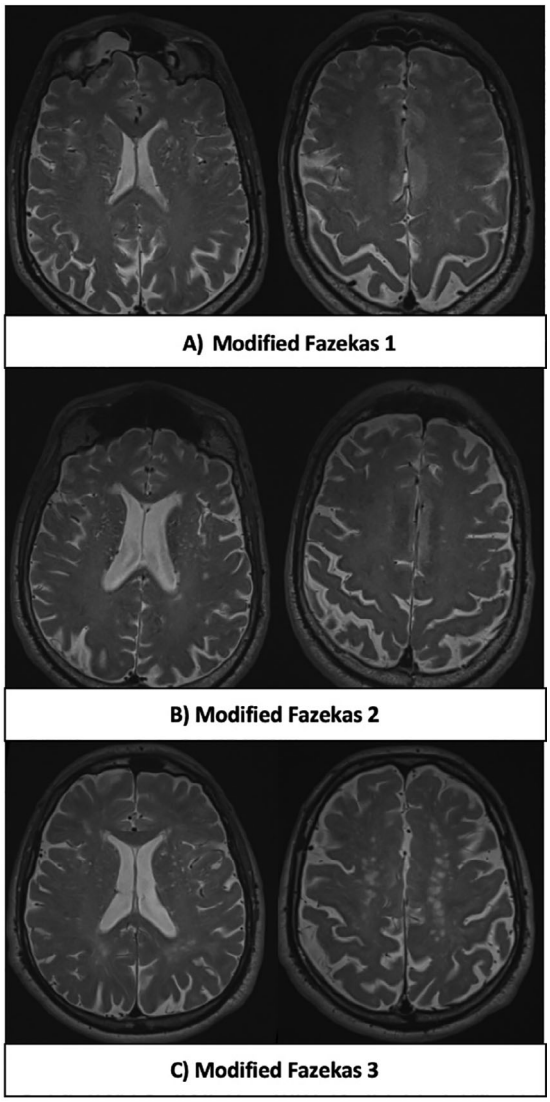

FIG. 1. Examples of LE with (**A**) mild, (**B**) moderate, and (**C**) severe manifestation.

without LE compared to the patient group with LE, but the difference was not statistically significant (mean: 5.36 ± 2.73 vs. 4.47 ± 2.26, $P = 0.09$).

Impact of Leucencephalopathy on Stimulation Efficacy and Complications of DBS

Mean preoperative UPDRS-III without medication (medication *off*) was 38 ± 11.6 points versus 14 ± 9.6 points (*t*-test $P < 0.0001$) under medication with the L-dopa challenge test (medication *on*). The median improvement in the L-dopa challenge test was 70% (95% CI 57.9–75). After DBS surgery, mean UPDRS-III without stimulation (stimulation OFF) was 42.5 ± 12.8 points versus 16.2 ± 8.6 points (*t*-test, $P < 0.0001$) under stimulation (stimulation ON). The median stimulation efficacy was 65.3% (95% CI 58.8–71.4). The mean surgical index in the study population was 1.1 ± 0.54. There was no correlation of LE with stimulation efficacy ($r = -0.05$, 95% CI −0.30 to 0.20, $P = 0.69$) or with surgical index ($r = -0.10$, 95% CI −0.30 to 0.11, $P = 0.35$). Postoperative hemorrhage occurred in 2.2% (3/135) of the included patients, whereas postoperative infection occurred in 7.5% (10/135). Postoperative computed tomography scans of the 3 patients with postoperative hemorrhage are shown in Figure 2. A higher incidence of LE did not correlate with postoperative hemorrhage ($r = 0.10$, 95% CI −0.06 to 0.26, $P = 0.24$). The incidence of LE did not correlate with postoperative infection ($r = -0.08$, 95% CI −0.25 to 0.08, $P = 0.30$). There was no correlation of the presence of LE with the number of used trajectories ($r = 0.06$, 95% CI −0.10 to 0.23, $P = 0.46$) or with the length of the STN signal in the MER ($r = 0.09$, 95% CI −0.07 to 0.12, $P = 0.27$). The median Evans ratio in the study population was 0.27 (95% CI 0.27–0.28), mean 0.27 ± 0.03, whereby ventriculomegaly with Evans ratio >0.30 was found in 22.2% (30/135). A higher incidence of LE correlated with a higher Evans ratio ($r = 0.29$, 95% CI 0.12–0.43, $P = 0.0006$).

TABLE 2 *Incidence of leucencephalopathy*

LE grading	Values
Original Fazekas scale periventricular white matter	
0	70/135 (51.9%)
1	57/135 (42.2%)
2	7/135 (5.2%)
3	1/135 (0.7%)
Original Fazekas scale deep white matter	
0	58/135 (43%)
1	45/135 (33.3%)
2	29/135 (21.5%)
3	3/135 (2.2%)
Modified Fazekas scale	
0	87/135 (64.4%)
1	31/135 (23%)
2	15/135 (11.1%)
3	2/135 (1.5%)

Discussion

This retrospective observational study was conducted to investigate the incidence of LE in PD patients undergoing DBS surgery and to evaluate its impact on surgical complications as well as on stimulation efficacy. One-third (35.6%) of the study population had

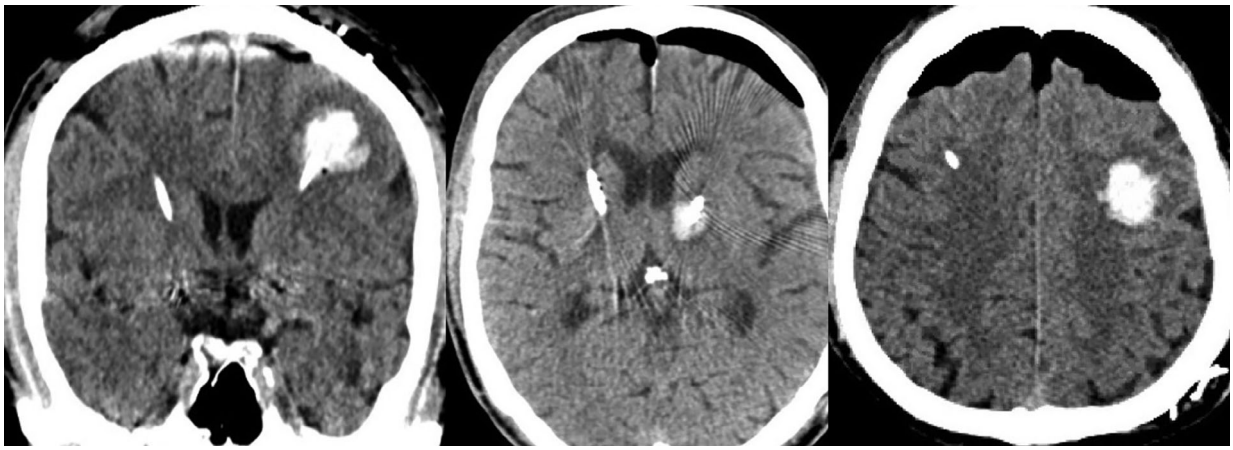

FIG. 2. Postoperative computed tomography scan showing postoperative hemorrhage after DBS (deep brain stimulation) surgery.

LE on preoperative MRI, and most had mild LE. LE was more prevalent in older patients, which was as expected because the incidence of LE increases with age.[15] An association of LE with motor impairment, especially with severe axial motor symptoms, but also with bradykinesia and rigidity, has been reported in previous studies.[6] However, there are no data in the literature currently about a possible interference of LE with surgical complications and motor improvement after DBS-STN surgery in PD patients, which was the rationale for conducting this study. The presence of mild to moderate LE was not associated with the occurrence of surgical complications of DBS surgery such as postoperative hemorrhage or infection. Nevertheless, all 3 patients experiencing postoperative hemorrhage had LE. Because only 1 patient in our study population was found to have severe LE, we still do not know whether severe LE contributes to a higher complication rate after STN-DBS in PD patients. The small overall incidence of postoperative hemorrhage in the study population (2%) may explain the lack of a significant correlation of LE with postoperative hemorrhage. This is clinically relevant because cerebral micro-bleeds have been associated with LE in previous studies.[16,17] However, most patients had mild LE, which may explain why LE was not associated with postoperative bleeding in our study; it occurred in only 3 of the 135 included patients. White matter lesions have often been reported to occur in association with movement disorders.[18,19] Previous studies show not only that LE is responsible for cognitive impairment in PD patients but also that it leads to a deterioration of motor function.[5,20–22] In our study, motor function was evaluated using the UPDRS-III. A surgical index based on the UPDRS-III was calculated to evaluate the effectiveness of DBS in improving motor function. There was no difference between surgical indices in patients with LE and those without LE. The presence of LE did not have an impact on the length of the STN signal during MER or on the number of used trajectories. White matter lesions have been previously reported to be associated with cognitive impairment in PD patients undergoing STN-DBS leading to a faster development of dementia.[23,24] Blume et al. therefore recommend to consider the presence of white matter lesion on preoperative imaging while planning STN-DBS in these patients.[23] In a retrospective study including 43 PD patients with STN-DBS, neuropsychological testing was performed preoperatively and 6 months postoperatively showing no correlation of cognitive decline with the volume of white matter lesions on imaging.[24] Unfortunately, no data concerning the cognitive function were available for our study population preventing correlation analysis of LE with cognitive impairment after STN-DBS.

There are several possible causes of LE, with small vessel cerebrovascular disease being the most common.[25] In our study, no data were available on the cause of LE; therefore, this could not be considered and should be addressed in future studies. According to the findings in our study, the presence of LE does not increase the risk for surgical complications and, is therefore, not a contraindication for performing a DBS surgery. The presence of mild to moderate LE, which was the case in one-third of our study population, was not associated with an increased risk for surgical complications—like postoperative hemorrhage or infection after DBS surgery—in PD patients. Furthermore, there was no significant difference in the improvement in long-term motor function with DBS between patients with and without LE. These findings show that mild to moderate LE is not a contraindication for performing DBS surgery in PD patients and has no negative impact on the efficacy of stimulation.

Limitations of the Study

Our study has several limitations due to the retrospective study design that led to the exclusion of patients for whom we had incomplete data. Another limitation is that only motor function was assessed, whereas data on nonmotor function were missing. Due to the retrospective design, no information was available concerning the cause of LE. Patients with severe LE were excluded from DBS treatment especially if they exhibited moderate cognitive impairment in the preoperative evaluation, which is a selection bias that needs to be considered.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution (2) Statistical analysis: A. Design, B. Execution, C. Review and critique (3) Manuscript preparation: A. Writing of the first draft, B. Review and critique.

P.J.: 1C, 1B, 2C, 3A
T.G.: 1C, 3B
C.D.: 1B, 3B
F.S.-D.: 1B, 2C, 3B
C.T.: 1B, 2C, 3B
B.M.: 1B, 2C, 3B
K.E.: 1B, 2C, 3B
D.M.: 1B, 2C, 3B
V.R.: 1B, 2C, 3B
V.M.: 1A, 1B, 2A, 2B, 3B

All authors reviewed the results and approved the final version of the manuscript.

Acknowledgments

Open Access funding enabled and organized by Projekt DEAL.

Disclosures

Ethical Compliance Statement: All patients or their next of kin signed a treatment contract in which they consented to the use of anonymized patient data for research purposes. The study was performed in accordance with our institution's ethical committee and the Helsinki Declaration. The study was approved by the local institutional review board, the Ethics Committee of the University Medical Center Göttingen (approval number: 10/6/21). We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: The authors declare that there are no additional disclosures to report. ■

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