Original Research Article

Induced micro lesion effect on cardinal motor features of Parkinson’s: A study with iMER signals of subthalamic-nuclei deep brain stimulations (Electrode-Implantation) by DBS

Venkateshwarla Rama Raju1,2,* , Srinivas Konda3, Kavitha Rani Balmuri3, Anvesh Balabhadra4

1 CMR College of Engineering & Technology, Kandlakoya, Medchal Rd, Hyderabad, Telangana, India
2 Fellow Neurology, Nizam’s Institute of Medical Sciences (NIMS), Hyderabad, Telangana, India
3 CMR Technical Campus, Kandlakoya, Medchal Rd, Hyderabad, Telangana, India
4 Gandhi Medical College, Secunderabad, Hyderabad, Telangana, India

A R T I C L E   I N F O

Article history:
Received 24-08-2020
Accepted 08-09-2020
Available online 18-09-2020

Keywords:
Deep brain stimulation (DBS)
Micro electrode recording (MER)
Micro lesion effect (MLE)
Parkinson’s disease (PD)
Subthalamic nuclei (STN).

A B S T R A C T

Induced micro lesion effect (μLE) on basic motor symptoms of Parkinson’s showing good results with the intra operative micro electrode recordings (iMER) of subthalamic-nuclei (STN) signals (patterns or signatures of STN) all through deep brain stimulations (DBS). MER-induced μLE was computed based on the difference between tremor, rigidity, and Bradykinesia (akinesia) scores in the pre op off-state and intra op on state following MER prior to test stimulus. To study the induced micro lesion effect on cardinal motoric feature-manifestations (symptoms) of Parkinson’s during the subthalamic nuclei deep brain stimulations by the intra operative microelectrode recordings. Clinical Relevance — stimulated intra operative microelectrode recordings micro lesion effect progressed the motor-manifestations of Parkinson’s. However, uncorrelated by the electrodes employed for the period of the process. MER-induced μLE was computed based on the difference between tremor, akinesia/Bradykinesia, and rigidity scores in the pre operative OFF state and intra operative state prior to stimulus-test experiment subsequent with micro electrode recording The MLE scores were enhanced by circa ~ 22% on Brains left hemisphere (BLH) and by ~14% on Brains right hemisphere (BRH) from zero line, i.e., electrical base line (p<0.05). Tremor scores were progressed by ~32% (BLH) and by 14% (BRH) and (p<0.05), rigidity scores improved by 17.3% (BLH) and by 14.2% (BRH) (p<0.05) and Bradykinesia scores improved by 20.6% (BLH) and by 11.5% (BRH) and (p<0.05) from baseline. There was no significant difference between μLE and the number of microelectrodes used (p>0.05). Stimulated intra operative microelectrode recordings and μLE progressed the motor-manifestations of Parkinson’s, yet, uncorrelated by the electrodes employed for the period of process.

© 2020 Published by Innovative Publication. This is an open access article under the CC BY-NC license (https://creativecommons.org/licenses/by-nc/4.0/)

1. Introduction

Deep brain stimulation or stimulator (DBS) is a surgical restorative therapy (therapeutic surgical procedure) for the patients of advanced idiopathic Parkinson disease (PD)1–8. Induced deep brain stimulations can be carried out by means of intra operative micro electrode signal recording (MER).9–12 However, detection of STN neurons signatures, i.e., patterns is difficult with sole DBS. The problem with targeting STN is that, it is a undersized (few millimeters in diameter - miniature size) biconvex lens almond shaped diamond structured, not visible while tracing through magnetic resonance imaging (MRI) as a result of lack of contrast among the STN and the adjoining–neighboring
brain sub-structures.\textsuperscript{8,9} The STN can be visualized on the MRI but other methods such as Lozano’s technique\textsuperscript{10} somewhere a point 3 mm lateral to the superolateral border of the red-nucleus is targeted have been observed and found to be successful regions’ for stimulus.\textsuperscript{10} The diameter of STN is extremely and exceedingly unpredictable, emerging to be designate slighter and to be found located more tangential and posterior—lateral on MRI images than in atlases. Hence, researchers must be concerned in relying on coordinates virtual to the commissures for targeting of subthalamic nuclei.

As the MRI techniques are not absolutely perfect, use of electrophysiological techniques such as microelectrode recording from the subthalamic nucleus as well as intraoperative stimulations can help in clearly demarcating the STN.

Microelectrode recording can identify subthalamic neurons by their characteristic bursting pattern and their signals clearly identify the nucleus form the surrounding structures. On table stimulation is studied to ensure that the there is optimal benefit with the least side effects and this is the final test to ensure the correct targeting of the STN.

Therefore, Micorecording (the microelectrode recording “MER”) is useful for identifying subthalamic-nuclei (STN) neurons patterns (“signatures”). The micro electrode signal recording can be adjuncified in the progress spontaneously of cardinal motor features of PD termed as “micro lesion effect.” Though, the fact accepted its impact on Parkinson disease motor features not known objectively. This study investigated fifty two subjects with Parkinson disease, particularly, with the micro-lesion-effect on motor signs and symptoms and its correlation with the pre operative L-Dopa (a metabolic precursor of dopamine chemical messengers) in STN-DBS surgery.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment in patients with Parkinson’s disease (PD).\textsuperscript{5,8,13} DBS can be performed with or without intraoperative microelectrode recording (MER).\textsuperscript{9–12} MER can be accompanied by spontaneous improvement of Parkinsonian motor symptoms, referred to as the microlesion effect (MLE).\textsuperscript{3} Although this phenomenon is widely recognized, its quantitative impact on motor symptoms is unknown. In this prospective study, the MLE on motor symptoms and its correlation with the preoperative levodopa response (LR) was investigated in 30 patients with PD who underwent DBS of the STN.

2. Objective

The aim is to study the effectiveness of MER and differentiate induced micro lesion result on cardinal motor feature-manifestations of Parkinson disease patients’ undergone subthalamic-nuclei deep brain stimulation.\textsuperscript{3} MER-induced MLE was evaluated based on the difference between tremor, rigidity, and bradykinesia scores in the preoperative off-state and intraoperative state following MER and before test stimulation.

Clinical Relevance—MER-induced MLE improved motor symptoms and was not correlated with the number of microelectrodes used during the procedure.

3. Methods and Materials

Fifty two subjects by means of Parkinson disease (PD) were included in the study. Subjects with advanced idiopathic PD of six years amid good response to L-Dopa (a metabolic precursor of dopamine) and Hoehn and Yahr (H & Y ) score of less than four through normal standard cognition (eligible for surgery) were incorporated in this study. Surgery was planned using a stereotactic Cosmon-Roberts-Wells (CRW) frame that has a luminant magnetic resonance image localizer. CRW frame with an MRI protocol using Medtronic five channel Framelink programming (encoding) software. By employing the micro electrode signal recording (MER) machine for the STN signatures (i.e., patterns) was executed in all subjects extending from 10 millimeters (mm) above target to 10 mm below the STN. Closing target medley was based on the effects and dyskinesias (side-effects) of induced macro stimuli (macrostimulation) and long-established by postoperative magnetic resonance imaging.

Study period was between the period of 2011–2017. Ethical clearance was obtained following HELSINKI principles.

3.1. Preoperative Examination

In all patients, tremor, rigidity, and Brdyskinesia were assessed according to the Unified Parkinson’s Disease Rating Scale (UPDRS) part III\textsuperscript{15} score in the preoperative off-state.

3.2. Surgery and intra operative microelectrode recording

52 subjects with PD were included in the study. Subjects with advanced PD of >5 years with good response to levodopa and H and Y score of <4 with normal cognition were eligible for surgery. Surgery was planned using a CRW frame with an MRI protocol using Framelink software with 5 channels. Microelectrode recording was performed in all subjects extending from 10 mm above target to 10 mm below STN. Final target selection was based on the effects and side effects of macrostimulation and confirmed by post op MRI.

Before the surgery (12 hours), the levodopa (antiparkinsonian-drugs) medication was off (med-off). All patients underwent preoperative magnetic resonance imaging (MRI) scanning, consisting of 1 millimeter T1 axial images, with and without gadolinium, and 2 millimeters T2-axial images (Siemens, 3–Tesla MR scanner, Erlangen,
3.4. Calculation of MLE

MER-induced MLE was calculated based on the difference in tremor, rigidity, and bradykinesia scores between the preoperative off-state and the intra-operative state following MER and before test stimulation.

3.5. Clinico—statistical analysis

Data are presented as mean ± SD. The SPSS Version 15.0 was used for statistical analysis. The data observed was abnormally distributed, and therefore, between-group differences were analyzed non-parametrically. The Wilcoxon signed ranks test was used to compare the motor scores in the preoperative off-state and the period after IM. The correlations between LR, age, and disease duration with the MLE were investigated using Spearman rho correlation test. p<0.05 was considered statistically significant. Micro-lesion-effect (with microrecording-induced) was assessed based on the difference between tremor, rigidity, and Bradykinesia scores in the preoperative off-state and intra operative state following MER and before test stimulation.

4. Results and Discussion

5. Results

Fifty nine Parkinson’s (Parkinson disease) subjects underwent the bilateral subthalamic-nuclei deep brain stimulation (STN-DBS) at our tertiary care hospital and research center in south India. Ethical clearance/approval obtained from the board following Helsinki principles. 59 needles (leads) were entrenched and 171 stimulus-electrodes applied for acquiring the signals of subthalamic nucleus (STN) neurons with microelectrode recording system (MER, 5 channels Framelink, Medtronic). In total 3 electrodes were exploited to acquire the STN neural data (MER signals of each neuron of dorsal STN). Subjects’ clinical demography - gender-allocation, mean-age, mean-age at the onset/ disease duration, and focal-margin is given in Table 1. Scores of Micro lesion were progressed by 13.6% in the right hemispheric brain (RHB) and 21.7% in the left-hemispheric brain (LHB) and statistically significant χ² @ 4.2857 for 1 degree of freedom, which significant at 5% with p ≤ 0.005. Table 2 shows the pre and intra operative scores recorded with MER system. There is a significant disparity seen in all motor sub scores in focal-margins assignable to micro lesion effect (significant at 5% (p<0.005, χ² @9.2958 with special attention to tremor and rigidity scores, which significantly increased and statistically significant at higher amplitudes. The correlation between post-DBS scores and MLE was assessed using Spearman rho correlation test. The Pearson’s r value for each parameter was calculated and statistically significant.
Discussion

The present study demonstrates that substantial MLE occurs following MER. In the literature, discussions on the mechanisms of MLE are limited and include those on perifocal edema, metabolic change, and local immunological reactions within the tissue around the electrode. Sitburana et al. have investigated MLE on essential tremor in patients with PD who underwent DBS of the thalamic ventral intermediate nucleus without MER. They had assessed solely the tremor response of MLE under the unilateral stimulation, and at the 6-month follow-up. In their study, three quarters of patients had a moderate-to-marked MLE. They concluded that MLE had minimal long-term clinical effects, except for allowing for lower DBS settings (patients with a marked MLE had mildly lower DBS parameters). In another study, Tykocki et al. have evaluated the MLE in patients with PD who underwent DBS of the STN, neither induced the behavioral disorder nor improved motor performance. They concluded that the STN is a complex and multifunctional structure, which integrates the motor, cognitive, and emotional components of basal ganglia-controlled behaviors.

Furthermore, we also observed that MLE had the greatest effect on bradykinesia symptoms. Effects on rigidity were less than those observed for both tremor and bradykinesia. However, these findings were inconsistent with Derrey et al.’s results, which demonstrated improvement rates of 42% (tremor), 37% (rigidity), and 25% (bradykinesia) from baseline.[4] Moreover, in Derrey et al.’s study, MLE was assessed on day 3 following DBS of the STN with MER, after at least 12 h of non-dopaminergic treatment, and before pulse generator placement. They found a 27% improvement ratio in the motor score (UPDRS part III) of MLE compared with baseline (off-state) levels.

In the present study, it was hypothesized that MLE is unrelated to the number of microelectrodes because the micro-electrodes were placed in the STN at a distance of 2 mm. The approximate STN size is as follows: AP: 5.9 mm, ML: 3.7 mm, and IS: 5 mm. Therefore, the motor part of the STN has less volume than the whole and a precise MER-related MLE is not accurately observed in the motor part because the electrodes were located in the limbic or associative parts of the STN. From an electrophysiological perspective, the motor part of the STN is not different from other parts of the STN. Because the limbic and associative side effects related to MLE following DBS of the STN were not evaluated in the present study, only the relation between the number of microelectrodes used and MLE was evaluated. STN is a small but crucial junction of the basal ganglia complex that has emotional, cognitive, and motor behavioral functions.

Table 1: Number of electrodes and data employed in the study (pre op)

| Parkinson Subjects | Gender | Maturity (Age) | Disease length (Yrs) | Response of Levedopa (Rol. %) | Principal Limit | # of electrodes |
|--------------------|--------|----------------|----------------------|-----------------------------|----------------|----------------|
| 30                 | M:19(63%) | 53±9          | 8.8±2.8              | 55±15                       | R:11(37%)      | L:19(63%)      | R: 2.9±1.2    |

2 degree of freedom). Tremor scores progressed (14.3% in RHB and 31.6% (p<0.05), followed by Bradykinesia (11.6% and 20.7%, p<0.05) and rigidity (14.3% and 17.4%, p<0.05) from baseline. MLE was more pronounced for tremor and Bradykinesia, compared to rigidity. Comparing with rigidity, micro-lesion-effect was marked more. Scores progressed on the whole were: RHB 13.7 and LHB 21.8% and also no significant difference among the electrodes used and micro-lesion-effect. Since the micro-lesion-effect score was high in LHB and hence no correlation was found among those two (p>0.05).

Conclusion

MER-induced MLE improved motor symptoms and was not correlated with the number of microelectrodes used during
the procedure. The results with respect to assumptions and design variables used in this study can be enlightened. Some of these parameters can be combined for an integrated parameter approach that may provide better insights for patient management.

8. Authors Contribution

This study designed and developed by the first author and substantial work was done by the rest of the authors.

9. Source of Funding

Grant # D. O. No. SR/CSRI/201/2016. Government of India, Ministry of Science & Technology (MST), Dept of Science & Technology (DST), Cognitive Science Research Initiative (CSRI), Technology Bhavan, New Mehrauli Rd., New Delhi.

10. Conflicts of Interest

None.

References

1. Alkmemade A, d Hollander G, Keuken MC, Schäfer A, Ott DVM, Schwarz J, et al. Comparison of T2*-weighted and QSM contrasts in Parkinson’s disease to visualize the STN with MRI. PLOS ONE. 2017;12(4):e0176130.

2. Cersosimo MG, Raina GB, Benaroch EE, Piedimonte F, Alemán GG, Micheli FE, et al. Micro lesion effect of the globus pallidus internus and outcome with deep brain stimulation in patients with Parkinson disease and dystonia. Mov Disord. 2009;24(10):1488–93.

3. Chiken S, Nambu A. High-Frequency Pallidal Stimulation Disrupts Information Flow through the Pallidum by GABAergic Inhibition. J Neurosci. 2013;33(6):2268–80.

4. Derrey S, Lefaucheur R, Chastan N, Gérardin E, Hannequin D, Desbordes M. Alleviation of off-period dystonia in Parkinson disease by a microlesion following subthalamic implantation. J Neurosurg. 2010;112(6):1263–6.

5. Deuschl G, Schade-Brittinger C, Krack P, Volkmann J, Schäfer H, Botzel K, et al. A Randomized Trial of Deep-Brain Stimulation for Parkinson’s Disease. N Engl J Med. 2006;355(9):896–908.

6. Fahn S, Members ER, Committee D. Unified Parkinson’s disease rating scale. In: S F, CD M, DB C, M G, editors. Recent Dev Parkinson’s Dis. vol. 2. Macmillan Health Care Information; 1987. p. 293–304.

7. Haberler C, Alesh F, Mazal PR, Pilz P, Jellinger K, Pinter MM, et al. No tissue damage by chronic deep brain stimulation in Parkinson’s disease. Ann Neurol. 2000;48(3):372–6.

8. Janssen MLF, Temel Y, Delaville C, Zwartjes DGM, Heida T, Deurwaerdère PD, et al. Cortico-subthalamic inputs from the motor, limbic, and associative areas in normal and dopamine-depleted rats are not fully segregated. Brain Struct Funct. 2017;222(6):2473–85.

9. Kocabicak E, Alptekin O, Ackermans L, Kubben P, Kuijf M, Kurt E, et al. Is there still need for microelectrode recording now the subthalamic nucleus can be well visualized with high field and ultrahigh MR imaging? Front Integr Neurosci. 2015;9(46).

10. Lozano CS, Ranjan M, Boutet A, Xu DS, Kucharczyk W, Fasano A, et al. Imaging alone versus microelectrode recording–guided targeting of the STN in patients with Parkinson’s disease. J Neurosurg. 2019;130(6):1847–52.

11. Mallet L, Schupbach M, N’Djaye K, Remy P, Bardinet E, Czernenecky V, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proce National Acad Sci. 2007;104(25):10661–6.

12. Sitburana O, Almaguer M, Ondo WG. A pilot study: Microlesion effects and tremor outcome in the ventrointermediate deep brain stimulation (VIM-DBS). Clin Neurol Neurosurg. 2010;112(2):106–9.

13. Maarouf M, Wojtecki L, Groiss S, Florin E, Sturm V, Fink G, et al. Clinical Outcome of Subthalamic Stimulation in Parkinson’s Disease is Improved by Intraoperative Multiple Trajectories Microelectrode Recording. J Neurol Surg Cental Eur Neurosurg. 2012;73(06):377–86.

14. Sun DA, Yu H, Spooner J, Tatsas AD, Davis T, Abel TW. Postmortem analysis following 71 months of deep brain stimulation of the subthalamic nucleus for Parkinson disease. J Neurosurg. 2008;109(2):325–9.

15. Tykocki T, Nauman P, Koziara H, Mandat T. Microlesion Effect as a Predictor of the Effectiveness of Subthalamic Deep Brain Stimulation for Parkinson’s Disease. Stereotact Funct Neurosurg. 2013;91(1):12–7.

16. Kocabicak D, Aygun D, Ozaydin I, Jahanshahi A, Onar M, et al. Does probe’s eye subthalamic nucleus length on T2W MRI reveals its role in the integration of the emotional and motor aspects of behavior. Brain Struct Funct. 2017;222(6):2473–85.

17. Odekerken VJ, v Laar T, Staal MJ, Mosch A, Hoffmann CF, Nijsen PC, et al. Subthalamic nucleus versus globus pallidus bilateral deep brain stimulation for advanced Parkinson’s disease (NSTAPS study):

| Table 2: Evaluation of pre op, intra post op motor scores of micro electrode recordings |
|----------------------------------------|--------|----------------|----------------|----------------|--------|--------|--------|--------|
| ToRH Score                            | ToLH Score | A/BoRH Score | A/BoLH Score | RoRH Score | RoLH Score | Full SoRH(Totality) | Full SoLH (Totality) |
| Preoperative Scores (on off medication) | 2.1±0.8 | 1.9±1.3 | 2.6±0.7 | 2.9±0.8 | 2.1±0.8 | 2.3±1 | 2.2±0.2 | 2.3±0.5 |
| Intra postoperative motor scores of MER | 1.8±0.9 | 1.3±1.2 | 2.3±0.7 | 2.3±0.8 | 1.8±0.9 | 1.9±1 | 1.9±0.2 | 1.8±0.5 |
| Progress %                             | 0.004  | 0.001  | 0.02   | 0.00   | 0.002  | 0.02  | 0.002  | 0.00   |

ToRH: Tremor on Right Hemisphere, ToLH: Tremor on Left Hemisphere, A/BoRH: Akinesia/Bradykinesia on Right Hemisphere, A/BoLH: Akinesia/Bradykinesia on Left Hemisphere, SoRH: Score on Right Hemisphere, SoLH: Score on Left Hemisphere.

\[ \chi^2 @ 4.2857 \text{ for } 1 \text{ df}, \text{ which significant at } 5\% \text{ with } p = 0.0283 \]

with a \[ \chi^2 @ 9.2857 \text{ with } 2 \text{ df}, \text{ highly significant at } 5\% \text{ with } p = 0.0045 \text{ highly significant.} \]

with a \[ \chi^2 @ 9.21 \text{ with } 2 \text{ df which is significant at } 5\% \text{ with } p =0.0015 \text{.} \]
a randomised controlled trial. *Lancet Neurol.* 2013;12(1):37–44.

**Author biography**

Venkateshwarla Rama Raju Senior Professor

Srinivas Konda Professor

Kavitha Rani Balmuri Professor

**Anvesh Balabhadra** Resident

Cite this article: Raju VR, Konda S, Balmuri KR, Balabhadra A. Induced micro lesion effect on cardinal motor features of Parkinson's: A study with iMER signals of subthalamic-nuclei deep brain stimulations (Electrode-Implantation) by DBS. *IP Indian J Neurosci* 2020;6(3):220-225.