



Research article

Relationship of brain edema after deep brain stimulation surgery with motor and cognitive function



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HIGHLIGHTS

- Peri-lead brain edema was sometimes developed after deep brain stimulation surgery.
- Development of frontal subcortical edema was related to transient cognitive decline.
- Peri sub-thalamic nucleus edema seemed associated with altered motor function.

ARTICLE INFO

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Parkinson's disease
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ABSTRACT

Background: Some patients with Parkinson's disease (PD) develop peri-lead brain edema after deep brain stimulation (DBS) surgery. The influence of edema on neurological function is not well characterized. We investigated the relationship of brain edema after DBS surgery with motor and cognitive function.

Methods: Thirteen patients with PD (6 males and 7 females; mean age: 61.2 years) who underwent bilateral subthalamic nucleus (STN) DBS surgery were included. All patients underwent magnetic resonance imaging (MRI) examination on day 6 post-DBS surgery. The volume of edema was measured either in the frontal white matter or STN on fluid attenuated inversion recovery (FLAIR) images. We examined the relationship between these volumes and changes in cognitive and motor function.

Results: Patients were divided into those with frontal subcortical edema (FE) $\geq 3,000$ mm³ (FE + group; n = 7) and $< 3,000$ mm³ (FE - group; n = 6). In the FE + group, the postoperative Mini-Mental State Examination score worsened by 2.4 points after one week compared with that immediately before surgery, while that in the FE - group worsened only by 0.2 points (p = 0.038). On comparing patients with peri-STN edema (SE) $\geq 1,000$ mm³ (SE + group; n = 3) and those with SE $< 1,000$ mm³ (SE - group; n = 10) showed that frequency of DBS tuning in the early postoperative period of the SE + group was lesser than that in the SE - group.

Conclusions: Development of FE after DBS surgery was related to transient cognitive decline. On the other hand, SE seemed associated with altered motor function and reduces the requirement for tuning in the initial period after DBS implantation.

1. Introduction

Deep brain stimulation (DBS) is an established therapy for Parkinson's disease (PD) [1]. However, patients who undergo DBS may experience side effects such as cerebrovascular disease, seizures, infection, depression, and postoperative cognitive impairment. Cerebral edema after DBS

surgery is not uncommon. In a study by Borellini et al, all 19 consecutive patients showed magnetic resonance imaging (MRI) signs of brain edema 7–20 days after surgery [2]. However, in another study, the incidence of cerebral edema at 6 weeks after surgery, as assessed by MRI, was 14.7% [3]. Jules et al reported brain edema in only 5.3% of 189 patients who underwent brain computed tomography (CT) at 3–8 days after surgery

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[4]. The detection rate may vary depending on the interval between the surgery and evaluation as well as on the detection method used (CT or MRI). Symptoms due to cerebral edema include headache, diplopia, seizure, and confusion. Many asymptomatic cases have also been reported, which were mostly evaluated by MRI for edema [2, 3, 4, 5, 6]. However, the frequency and the clinical impact of edema have not been fully explored.

Micro lesion effect (MLE) is the effect of surgical implantation on the intended DBS target and the surrounding structures as a result of the passage of recording or stimulating electrodes. MLE has been shown to influence the outcomes of DBS therapy [7]. Therefore, peri-STN edema may affect motor symptoms through MLE.

In the present study, we investigated the frequency and the extent of edema in patients who underwent an MRI scan along the clinical pathway on the 6th postoperative day. We also aimed to determine the effects of edema on cognition and motor function.

2. Materials and methods

2.1. Participants

In this study, we retrospectively evaluated 13 consecutive patients with PD who underwent bilateral STN DBS surgery between January 2018 and November 2018. Postoperative MRI study was performed at 6 days and at 3 months after DBS surgery. All participants provided written informed consent for participation in the study. The study was conducted according to the Declaration of Helsinki and approved by the Ethical Review Board of the Mie University Hospital (3148) and the Suzuka Kaisei Hospital (2016–05).

2.2. Surgery procedures

All patients underwent bilateral electrode placement for STN DBS. Electrodes (VERCISE CARTESIA™ DIRECTIONAL LEAD, Boston Scientific, Natick, MA, USA) were implanted under local anesthesia using a Leksell stereotactic frame (Elekta Instruments AB, Stockholm, Sweden) and anatomical (MRI and CT) and physiological targeting. Based on microelectrode recordings, electrodes were considered correctly located in the target region. All electrode were implanted by single trajectory. Impulse generators (Vercise Gevia, Boston Scientific) were implanted and connected during a second surgical procedure on the same day [8].

2.3. MRI data acquisition and analysis

All MRI images after DBS surgery were obtained using a 1.5T MR unit (Ingenia; Philips Healthcare, Best, The Netherlands). The pulse sequence used for T1-weighted image (T1WI) was a three-dimensional turbo field-echo (TFE) technique with the following parameters: repetition time: 8.2 ms; echo time: 4.2 ms; TFE factor: 40; field of view: 240 mm; matrix size: 240 × 240 (pixel size 1.00 × 1.00 mm); slice thickness: 1.6 mm; Recon voxel size: 1.00 × 1.00 × 0.80; 1-averaged: 220 slices; and acquisition time: 4 min, 29 s fluid attenuated inversion recovery (FLAIR) image was a three-dimensional turbo spin-echo (TSE) technique with the following parameters: repetition time: 4,800 ms; echo time: 421 ms; inversion time: 1,660 ms; TSE factor: 178; field of view: 260 mm; matrix size: 236 × 236 (pixel size 1.10 × 1.10 mm); slice thickness: 1.14 mm; Recon voxel size: 0.51 × 0.51 × 0.57; 1-averaged: 305 slices; and acquisition time: 6 min, 24 s. The pulse sequence used for diffusion-weighted image (DWI) technique had the following parameters: repetition time: 5,335 ms; echo time: 95 ms, single shot; field of view: 230 mm; matrix size: 128 × 154 (pixel size 1.80 × 1.49 mm); slice thickness: 5.00 mm; Recon voxel size: 0.90 × 0.90 × 5.00; 1-averaged: 23 slices; and acquisition time: 1 min, 4 s. The pulse sequence used for susceptibility-weighted image (SWI) technique had the following parameters: repetition time: 30 ms; echo time: 44 ms; field of view: 230 mm; matrix size: 288 × 288 (pixel size 0.80 × 0.80 mm); slice thickness: 0.80 mm; Recon voxel size: 0.41 × 0.41

Table 1. Patient profile.

	Pre-operation	After 1 week	After 3 months
Age	61.2 ± 10.2	-	-
Sex (M:F)	6:7	-	-
Disease duration (years)	13.3 ± 7.8	-	-
DBS target	STN 13	-	-
Hoehn-Yahr stage (on state)	2.7 ± 0.9	2.3 ± 1.1	2.0 ± 0.9
Hoehn-Yahr stage (off state)	3.8 ± 0.8	2.5 ± 1.0**	2.2 ± 0.9**
MDS-UPDRS Part I	9.4 ± 5.2	5.2 ± 3.4*	5.5 ± 4.1
MDS-UPDRS Part II	10.0 ± 6.2	8.2 ± 7.8	5.4 ± 3.7
MDS-UPDRS Part III(on state)	16.6 ± 12.2	15.8 ± 13.9	7.1 ± 5.7*
MDS-UPDRS Part III(off state)	38.7 ± 18.6	-	19.8 ± 16.3*
MDS-UPDRS Part IV	10.9 ± 4.8	3.5 ± 3.6**	3.2 ± 3.1**
LEDD (mg)	924.9 ± 247.8	505.5 ± 168.1**	491.2 ± 175.8**
L-Dopa (mg)	457.7 ± 178.9	305.8 ± 100.0*	315.4 ± 101.3*
DA (use rate; %)	100	76.9	76.9
Entacapone (use rate; %)	84.6	46.2	46.2
Selegiline (use rate; %)	53.8	46.2	46.2
Zonisamide (use rate; %)	46.2	53.8	53.8
MMSE	28.2 ± 1.7	26.8 ± 2.6	28.2 ± 1.8
MoCA-J	25.2 ± 2.3	23.7 ± 3.7	26.1 ± 2.5
FAB	15.8 ± 2.2	15.6 ± 2.0	16.7 ± 1.2
TMT-A (s)	136.3 ± 58.4	150.6 ± 53.2	125.7 ± 45.0
TMT-B (s)	187.6 ± 86.4	232.5 ± 124.5	178.8 ± 104
CED-D	16.2 ± 7.8	14.0 ± 11.0	10.8 ± 10.3

*p < 0.05, **p < 0.01 compared to the Pre-operation.

DBS, deep brain stimulation; STN, subthalamic nucleus; GPi, internal segment of globus pallidus; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; DA, dopamine agonist MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of Montreal Cognitive Assessment; FAB, Frontal Assessment Battery; TMT, Trail Making Test; CES-D, the Center for Epidemiologic Studies Depression Scale.

× 0.80; slice gap: -0.8 mm, 1-averaged, 170 slices; and acquisition time: 4 min, 35 s. These are the officially accepted parameters for post-DBS surgery MRI examinations in Japan.

The volume of brain edema was calculated using FLAIR. For assessing the frontal subcortical edema (FE), we first reconstructed the axial images from sagittal FLAIR sequences with the thickness of 5 mm. Second, we manually determined the high signal area of each slice of FLAIR images and measured its area. Third, we calculated volume by the area and thickness. For the peri-STN edema (SE), we first reconstructed the axial images from sagittal FLAIR with the thickness of 2 mm. Second, we manually determined the high signal area of each slice of FLAIR images and measured its area. Third, we calculated volume by the area and thickness.

FE was divided into two groups with reference to the median, with 3,000 mm³ or more being the FE + group and less than 3,000 mm³ being the FE-group. Since there were many cases in which SE did not exist at all and grouping by median was inappropriate, we divided it into SE + group and SE-group at 1,000 mm³ based on visual evaluation by two specialists.

2.4. Patients data analysis

All patients were assessed using the Japanese version of the Movement Disorder Society Revision of the Unified PD Rating Scale (MDS-UPDRS), Mini-Mental State Examination (MMSE), Japanese version of Montreal Cognitive Assessment (MoCA-J), and the Trail Making Test at 3 time-points: before DBS (i.e., baseline); 10 days postoperatively; and 3 months postoperatively [9, 10, 11, 12]. The levodopa equivalent daily dose for each patient was calculated as follows: 100 mg L-dopa/decarboxylase inhibitor = 1 mg pramipexole

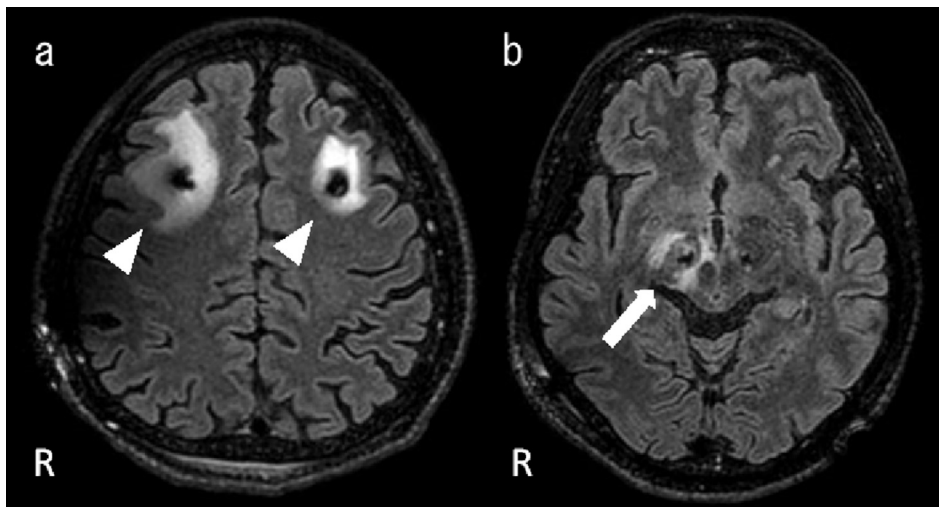


Figure 1. Representative cases of post-DBS edema (72-year-old patient). (a) Frontal edema (arrow head). (b) Peri sub-thalamic nucleus (STN) edema (arrow). He underwent bilateral STN-DBS surgery and had no subjective side effects, but MRI scan performed 6 days after surgery revealed edema around the lead. In our measurement method described in the text, FE was 21,012 mm³ on the right side, 6,326 mm³ on the left side, and SE was 3,856 mm³ on the right side and 136 mm³ on the left side.

= 1 mg pergolide mesylate = 5 mg ropinirole = 7.5 mg/day rotigotine = 1.5 mg cabergoline = 70 mg L-dopa/decarboxylase inhibitor with entacapone = 10 mg selegiline = 100 mg amantadine [13]. Electrical stimulation for all patients was started on the day of surgery. Tuning of electrical stimulation was made as required in response to changes in symptoms. The frequency of tuning was counted up to 90 days after DBS surgery.

2.5. Statistical analysis

The Mann-Whitney U-test (two tails) was used to compare various scores pre and post operation, and to compare the two groups according to the degree of edema. Inter- and intra-rater reliability was measured using two-way random average measure and one-way random single measure Intraclass Correlation Coefficient (ICC) and the associated 95% confidence intervals (CIs). All statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY). An α level of 0.05 was used to infer significance for all statistical tests. In area analysis, the intra-rater ICC for the frontal edema was 0.998 [95% CI 0.994–0.999, $p < 0.001$] whereas the inter-rater ICC for the frontal edema was 0.977 (95% CI 0.929–0.993, $p < 0.001$). The intra-rater ICC for the SE was 0.971 (95% CI 0.911–0.991, $p < 0.001$) whereas the inter-rater ICC for the SE was 0.929 (95% CI 0.793–0.978, $p < 0.001$).

3. Results

The study population comprised of 6 males and 7 females. The average age of patients and average disease duration were 61.2 ± 10.2 and 13.3 ± 7.5 years, respectively. The average MMSE and MoCA-J scores at baseline were 28.2 ± 1.7 and 25.2 ± 2.3 points. The average MDS-UPDRS part III scores at on and off state were 16.6 ± 12.2 and 38.7 ± 18.6 , respectively (Table 1). The average motor performance at 3 months after DBS was significantly better than that at baseline. Hoehn Yahr stage (on state) improved from 2.7 ± 0.9 to 2.0 ± 0.9 ($p = 0.10$), and Hoehn Yahr stage (off state) improved from 3.8 ± 0.8 to 2.2 ± 0.9 ($p = 0.002$). UPDRS part III (on state) improved from 16.6 ± 12.2 before surgery to 7.1 ± 5.7 ($p = 0.032$), and part III (off state) improved from 38.7 ± 18.6 to 19.8 ± 16.3 ($p = 0.021$). The MMSE and MoCA-J scores at 3 months after DBS surgery (28.2 ± 1.7 and 25.2 ± 2.3 , respectively) were not significantly different from those at baseline (28.2 ± 1.8 and 26.1 ± 2.5 ; $p = 0.56$ and 0.43 , respectively).

No bleeding complication was observed in this study on SWI. FLAIR sequences obtained at 6 days after DBS showed brain edema in 10 of 13 cases (77%). Seven out of the 10 patients with brain edema had both frontal and peri-STN area edema (Figure 1), while the remaining 3 patients had only frontal subcortical edema. In all cases, the brain edema was completely resolved at 3 months.

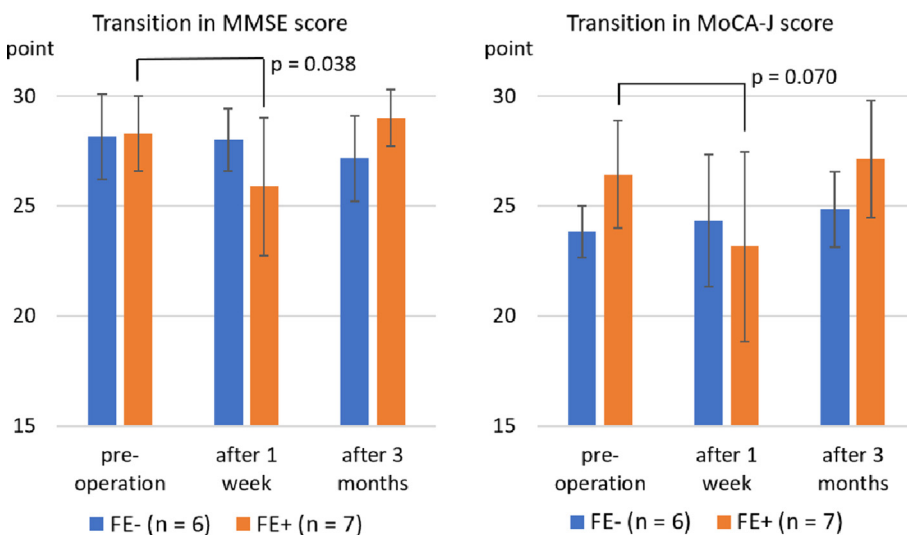


Figure 2. Transition in MMSE and MoCA-J score in FE+ and FE-group. In the FE + group, the average postoperative MMSE score worsened by 2.4 ± 2.4 points after one week compared with the pre-operation level, while that in the FE-group worsened only by 0.2 ± 1.5 points ($p = 0.038$). The MoCA-J score worsened by 3.3 ± 4.8 points after one week compared with the pre-operation level, while the FE-group showed improvement in MoCA-J score by -0.5 ± 2.9 points ($p = 0.070$). However, 3 months after the operation, MMSE and MoCA-J score of the FE + group improved to the same level as before the operation.

Table 2. Comparison of the FE+ and FE-groups from pre to after 1week operation.

(pre-operation)- (after 1 week operation) score	FE + group (n = 7)	FE- group (n = 6)	p value
Hoehn-Yahr stage (on state)	0.1 ± 0.4	0.67 ± 1.0	0.49
Hoehn-Yahr stage (off state)	1.5 ± 0.5	1.3 ± 0.8	0.40
MDS-UPDRS Part I	4.1 ± 5.1	4.3 ± 7.4	0.59
MDS-UPDRS Part II	4.4 ± 6.8	-1.0 ± 6.6	0.20
MDS-UPDRS Part III (on state)	-1.1 ± 5.7	3.2 ± 24.4	0.52
MDS-UPDRS Part IV	9.4 ± 4.1	5.0 ± 3.5	0.11
MMSE	2.4 ± 2.4	0.2 ± 1.5	0.038
MoCA-J	3.3 ± 4.8	-0.5 ± 2.9	0.070

MDS-UPDRS, Movement Disorder. Society Unified Parkinson's Disease Rating Scale; MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of Montreal Cognitive Assessment.

We divided the 13 patients into those with frontal subcortical edema (FE) $\geq 3,000 \text{ mm}^3$ (FE + group; n = 7) or $< 3,000 \text{ mm}^3$ (FE-group; n = 6). In the FE + group, the average postoperative MMSE score worsened by 2.4 ± 2.4 points after one week compared with the pre-operation level, while that in the FE-group worsened only by 0.2 ± 1.5 points ($p = 0.038$). In the FE + group, deterioration in the MMSE sub-items were observed only in "orientation to time (average 0.86 points decrease)," "delayed recall (average 0.57 points decrease)," and "serial 7 subtraction (average 1.1 points decrease)." In the FE + group, the MoCA-J score worsened by 3.3 ± 4.8 points after one week compared with the pre-operation level, while the FE-group showed improvement in MoCA-J score by -0.5 ± 2.9 points ($p = 0.070$) (Figure 2). The most noticeable deterioration in the FE + group was in "delayed recall." However, 3 months after the operation, MMSE and MoCA-J score of the FE + group improved to the same level as before the operation. The amount of decrease in MMSE score 3 months after the operation was -0.7 ± 0.8 points in the FE + group and 1.0 ± 2.3 points in the FE-group ($p = 0.25$). Similarly, the amount of decrease in MoCA-J score was -0.7 ± 2.1 points in the FE + group and -1.0 ± 1.7 points in the FE-group ($p = 0.57$). There was no significant difference between the FE+ and FE-groups with respect to MDS-UPDRS score at 1 week or at 3 months (Table 2).

We divided the 13 patients into those with peri-STN edema (SE) $\geq 1,000 \text{ mm}^3$ (SE + group; n = 3) or $< 1000 \text{ mm}^3$ (SE-group; n = 10). Then, we defined three periods: period I (1–20 days after surgery), period II (21–90 days after surgery) and measured the frequency of DBS tuning within each period. Within the period I, average frequency of DBS tuning in the SE + group was significantly less than that in the SE-group (0.46 ± 0.20 vs. 1.68 ± 0.77 times per week, $p = 0.047$) (Figure 3). Within the period II, there was no significant between-group difference in this respect (0.6 ± 0.2 vs. 0.33 ± 0.18 times per week, $p = 0.086$).

In two patients, DWI exhibited high intensity located at the medial side of the implanted lead after 1 week. None of these two cases showed any new neurological deficit such as clinical paralysis. After 3 months, in T1WI, we observed low intensity in the same area (Figure 4).

4. Discussion

The reported incidence of brain edema after DBS surgery ranges from 3.2% to 100% [2, 4, 6, 14]. In previous studies, there was much variability with respect to the imaging modality used (CT or MRI) and the timing of imaging. In this study, we evaluated the results of MRI performed at 6 days and 3 months after DBS. On MRI images obtained at 6 days after DBS, 10 of 13 patients (77%) showed brain edema; all these patients showed complete resolution of edema in MRI images obtained at 3 months. The postulated pathophysiological mechanisms of edema include role of infection, irrigating solutions used during the surgical

Frequency of DBS tuning (Times / week)

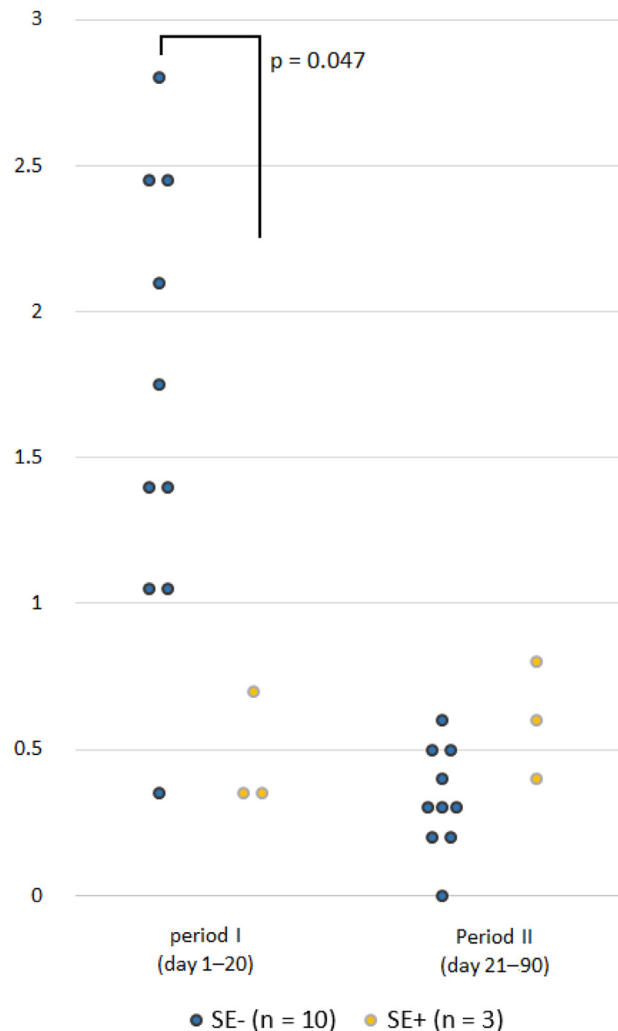


Figure 3. Frequency of DBS tuning. Within the period I, the average frequency of DBS tuning in the SE + group was lesser than that in the SE-group. That is, peri-STN edema reduces the requirement for DBS tuning in the initial period after DBS implantation.

procedure, cerebral venous infarction, breakdown of blood-brain barrier due to micro-hemorrhages or mechanical trauma, MER-guided implantation, and allergy [15]. However, the precise cause is yet to be elucidated. Based on the analysis of contrast-enhanced CT and contrast-enhanced T1WI (CE-MRI), Saitoh et al described two main types of edema: (1) limited edema in the deep white matter likely associated with micro vessel occlusion; (2) extensive edema in the surface white matter likely associated with other mechanisms owing to the lack of detection of micro vessel occlusion [5].

Of note, in the present study, two patients exhibited high intensity in DWI on the 6th day after DBS, and they both exhibited hypointensity in T1WI 3 months after DBS. This pattern of change is consistent with that of small cerebral infarction [16]. Based on the site (periventricular region; located on medial side of the implanted lead) and morphology of the lesion, this was likely attributable to the physical compression of the blood vessels running through the medulla by the leads [17]. No clinical deterioration was observed in either of the patients. In a study by Fenoy et al, only 3 out of 728 patients developed cerebral infarction after DBS operation; however, it is entire plausible that many asymptomatic cerebral infarctions may have remained undetected in the absence of routine

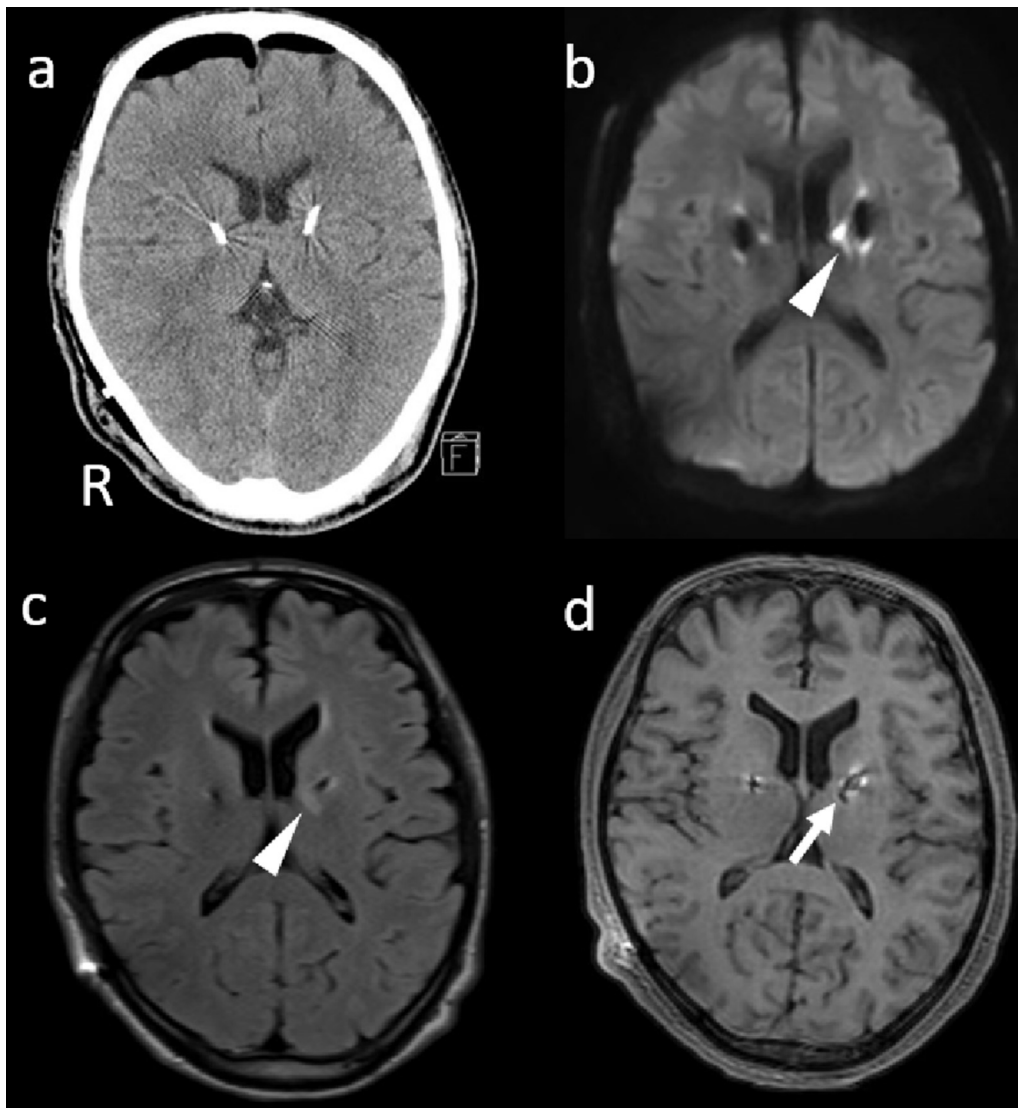


Figure 4. Cerebral infarction after DBS operation. Two patients (44-year-old man and 68-year-old man) developed cerebral infarction after DBS operation, although neither of them had any subjective symptoms. Both of them had no FE and SE at all. Images of a representative case (44-year-old man) are shown. (a) It is difficult to identify the lesion even retrospectively on the CT image obtained immediately after the operation due to the small size of the lesion and the artifact. (b, c) High-intensity area at the medial side of the implanted lead is observed on diffusion-weighted imaging and FLAIR after 1 week operation (arrow head). (d) T1WI image at 3 months shows low intensity in the same area (arrow).

MRI examination. Since no obvious edema occurred in the two cases, it was suggested that the cause of deep white matter edema may not be explained by vascular occlusion alone, and that it was a pathological condition caused by multiple factors.

In our study, the FE + group experienced transient cognitive decline; however, the cognitive function returned to normal after 3 months. Previous reports have described symptoms associated with edema; however, none of these studies have mentioned cognitive scores. This report is the first to examine the detailed cognitive profile of patients.

In the SE + group, the period required for DBS tuning was longer than that in the SE-group, and it can be interpreted that MLE occurs in the SE + group during the period I. SE may have affected the temporal profile of MLE. Actually, even in the absence of any abnormal CT findings, MRI was able to delineate SE in this study; therefore, it may not necessarily be appropriate to designate “micro” lesion effect.

Some limitations of our study should be acknowledged. First, the number of patients was insufficient. Second, the precise timing of development and subsidence of cerebral edema is not clear since we performed MRI assessments at only two time-points (at one week and at 3 months). Future studies should include MRI assessment at various time-points to address this issue. Third, the pathology was not examined, and the correct diagnosis is unknown. Fourth, since this was a retrospective study, the motor scores were not evaluated in a drug-free state; therefore,

it is difficult to assess the MLE. These issues should be addressed in future investigations.

Declarations

Author contribution statement

Yamato Nishiguchi, Keita Matsuura: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Yoshinori Hirata, Akane Mizutani, Natsuko Katoh, Hidehiro Ishikawa, Koichi Miyashita, Takaya Utsunomiya, Hiroyuki Kajikawa: Contributed reagents, materials, analysis tools or data.

Hirofumi Nishikawa, Tomohiro Araki: Performed the experiments.

Akihiro Shindo, Hidekazu Tomimoto: Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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