



# Surgical-Related and Hardware-Related Adverse Effects of Deep Brain Stimulation: A Retrospective Single-Center Analysis

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## ABSTRACT

**AIM:** To review both the surgical-related, and hardware-related adverse effects of deep brain stimulation (DBS) in a single center over the last five years.

**MATERIAL and METHODS:** All patients who underwent DBS electrode implantation at the Akdeniz University Hospital during the last five years participated in this study. Demographic information (sex, age, diagnosis, the duration between diagnosis and surgery, comorbid disease) and the date of surgery were collected from an electronic medical database. The adverse effects of DBS were classified into two: surgery-related and hardware-related effects, which were further subdivided based on whether they occurred intraoperatively, in the early postoperative stage, or over a long period time.

**RESULTS:** A database of 47 patients with 90 DBS electrode implants was analyzed in the study. The median age at the time of surgery of all patients was 54 years (range 11–75). Comorbid diseases were recorded in 16 (34%) patients. Out of the total, 33 patients (70.2%) had no adverse effects related to DBS. Surgical-related adverse effects were observed in five patients and of these, one had an asymptomatic intracerebral hemorrhage (ICH), one had symptomatic ICH, one had both a seizure intraoperatively and an asymptomatic subdural hematoma whereas the other two had non-infectious peri-electrode edema. Hardware-related adverse effects were recorded in nine patients (19.1%). We recorded infections in six (12.7%) patients, erosion without infection in two (4.2%), and both lead fracture and lead malposition in one patient. All long-lasting adverse effects were hardware-related and recorded in eight (19%) patients.

**CONCLUSION:** DBS has been a well-established treatment for movement disorders but is associated with an increased risk of some adverse events which have been analyzed in this study.

**KEYWORDS:** Deep brain stimulation, Hardware-related, Surgical-related, Complications, Infection, Peri-lead edema

## INTRODUCTION

Deep brain stimulation (DBS) is a surgical treatment method used for the chronic electrical stimulation of a potential brain target through an implanted electrode. It has been established as an effective, reversible treatment for movement disorders such as dystonia, Parkinson's disease (PD), and essential tremor (ET), especially for patients with refractory symptoms to medicine and/or unendurable

adverse effects from them. The potential targets of DBS are the subthalamic nucleus (STN) or globus pallidus interna (GPI) for PD, ventral intermediate nucleus (VIM) of the thalamus for tremor, and GPI for dystonia. Many adverse effects associated with DBS have been reported in the literature, although it is known to be a less invasive, safe, and reversible surgical treatment. The number of complications is also increasing with the widespread use of DBS surgery in the world (42), the adverse effects of which can be related to surgical, hardware, and

stimulation. Surgical-related and hardware-related complications can cause serious morbidity and mortality, while stimulation-related adverse effects can be eliminated by turning the stimulation off or changing the stimulation program. The most common surgical adverse effects of DBS have been reported as asymptomatic or symptomatic intracranial hemorrhage (ICH) (15,17,28). The hardware involved in DBS consists of parts containing an internal pulse generator (IPG), multi-contact intracranial lead, and connector or extension cable. The effects related to any part of the hardware and/or body part in direct contact with them are classified as hardware-related adverse effects. Infections, lead fracture, skin erosion with or without infection, and IPG malfunction are the most common hardware-related complications from the procedure (8,21,25). This study was to report the surgical-related and hardware-related adverse effects of DBS in a single center over the last five years.

## ■ MATERIAL and METHODS

This retrospective study was approved by the University of Akdeniz Ethics Committee (KAEK-561). All participants signed their informed consent for data collection during the follow-up visits. All patients who underwent DBS electrode implantation at the Akdeniz University Hospital during the five years from March 2015 to June 2020 participated in this study. All surgeries were performed by the same neurosurgeon (T.U). Demographic information (sex, age, diagnosis, the duration between diagnosis and surgery, comorbid disease) and the date of surgery were collected from an electronic medical database. The Unified Parkinson's Disease Rating Scales (UPDRS) were recorded of the patients with PD before DBS and six months after the surgery. Before surgery, subjects with PD were tested on and off the levodopa medication condition. On medical condition was accepted as at least an hour after taking their usual levodopa dose while the off medical condition was accepted as at least 12 hours without taking their anti-Parkinson medications. PD patients were evaluated with the UPDRS again six months after surgery in both the on and off medical conditions when the DBS stimulators were on.

The adverse effects of DBS were classified into surgery-related adverse effects which were directly due to the procedure and hardware-related adverse effects which were due to any parts of the hardware and/or body parts (e.g., skin, brain) in direct contact with them. Subsequently, these effects were subdivided based on when they occurred: intraoperative, early postoperative stage (within one month of the operation), or long term (at least one month after implantation).

For infection adverse effects, the location of the infection and culture results were collected. The management of infections related to DBS, including antibiotic treatment, local surgical repairment, and removal of hardware, was also examined.

### Surgical Procedure

Contrast-enhanced T1 and T2-weighted magnetic resonance images (MRI) were taken one day before the surgery. The target selection for the placement of the contacts was performed at the level of maximal rubral diameter (around 5mm below the

AC-PC plane) using commercially available planning software (Framelink 5, Medtronic, Minneapolis). We carefully planned the DBS lead trajectory to prevent the DBS leads from passing through the blood vessels, sulci, or ventricles. The entry point was defined at or behind the coronal suture. Our targets were GPI in dystonic patients, bilateral STN in all PD, and VIM in all patients with tremors.

On the morning of the operation, the Leksell Stereotactic G-frame (Elekta Instrument AB, Stockholm) was placed on the patient's head under local anesthesia. The patient's non-contrast brain tomography (CT) with a slice thickness of 1 mm was taken and CT images were transferred to the planning software to be fused to the MRI images. These images were coordinated to the system of the Leksell G-frame (Elekta Instrument AB, Stockholm). The target was defined with direct visualisation and then corrected with standard target coordinates. After local anesthesia, a curvilinear skin incision was made and a burr hole was created along the planned DBS lead trajectory. Microelectrode recording (MER) (Lead point, Medtronic Minneapolis,) was performed to ensure precise targeting. Macrostimulation on the target selected with MER was performed to evaluate if there were any adverse effects and/or improved symptoms associated with the stimulation. We implanted DBS electrodes (Lead model 3387 and 3389, Medtronic, Minneapolis, USA) in the determined area as the correct target under local anesthesia, except for two dystonia cases. The electrodes were secured in place with a skull fixation device (Medtronic burr hole cap or Stimloc device). On the same day of the DBS electrode implantation, after general anesthesia, IPGs (Activa PC Medtronic) were implanted in the subfascial layer of the pectoral muscles of 42 patients and abdominal muscles of five patients. The positions of the electrodes on post-operative CT scans were compared with preoperative MR images for correction. The DBS programming was initiated approximately one week after surgery.

### Statistical Analysis

Quantitative data were presented with median value and range, and qualitative data presented as absolute numbers and percentages. In order to assess the difference between categorical variables, the chi-square test was employed. In the crosstabs, if the expected value was less than five in at least one cell, Fisher's exact test was used. The normal distribution of the data was examined using the Shapiro-Wilk normality test. The Mann-Whitney U test was applied to determine whether there was a statistically significant difference between the two independent groups. A value of  $p < 0.05$  was used to assess the significance for all statistical analyses. The statistical analysis was carried out with the IBM SPSS Version 21.0 (SPSS Inc., IL-USA) software.

## ■ RESULTS

A database of 47 patients with 90 DBS electrode implants was analyzed in the study. Thirty (62%) of the patients were male and the median age of all patients at the time of surgery was 54 years (range 11–75). The participants consisted of 30 patients with PD, 13 with dystonia, three with rubral tremor,

**Table I:** Demographic Features and Diagnoses of Patients and Targets of Implantation

Disease	Age median	Sex female/male	Disease duration median (years)	STN Bil	Vim Uni	Vim Bil	GPI Uni	GPI Bil
PD n=30	56	10/20	10	30				
Distoni n=13	38	5/8	15				1	12
ET n=1	75	Male	30			1		
Rubral tremor n=3	35	2/1	6		3			

**PD:** Parkinson's Disease, **ET:** Essential tremor, **STN:** Subthalamic nucleus, **GPI:** Globus pallidus interna, **VIM:** Ventral intermediate nucleus, **Bil:** Bilateral, **Uni:** Unilateral.

**Table II:** All Adverse Events of the Patients

Adverse events	n (%)
Symptomatic ICH	1 (2.1)
Asymptomatic ICH	1 (2.1)
Subdural hemorrhage	1 (2.1)
Perielectrode edema	2 (2.1)
Infection	6 (12.7)
Erosion without infection	2 (4.2)
Lead fracture and lead malposition	1 (2.1)

**ICH:** Intracerebral haemorrhage.

and one with ET. The median follow-up period was 28 months (range 6–71).

The median age of the patients with PD at the time of implantation of DBS was 56 years (r: 40–70) and the mean duration time between the diagnosis and surgery was ten years. The PD subjects had a comparable UPDRS part III (motor score), with  $30.2 \pm 7.1$  and  $64.1 \pm 19.4$  at the baseline and  $18.6 \pm 9$  and  $36.7 \pm 18$  six months after the DBS surgery when the DBS stimulators were on (on and off levodopa medical conditions, respectively).

At the time of DBS implantation, the median age of the patients with dystonia was 38 and two of these dystonic patients were under 18. Eight of the dystonic patients had generalised dystonia. Secondary dystonia was recorded in six (46.1%) patients; one with pantothenate kinase-associated neurodegeneration (PKAN), three with cerebral palsy, one with drug-induced Pisa syndrome, and one with a history of cardiac arrest due to using Bonzai. Two dystonic patients with cerebral palsy additionally had baclofen pumps due to spasticity. In the dystonic patient group, the median period between the diagnosis and implantation of DBS was 15 (r:3-37) years. The patients with rubral tremors had a history of post-traumatic or spontaneous ICH and, thus, unilateral

VIM DBS was performed in these patients. In the group of patients with rubral tremors, the median age at surgery and the period between the diagnosis and surgical process was 35 and six years respectively. The bilateral VIM-DBS implantation was performed in a 75-year-old male patient with ET. Table I presents details of the demographic features and diagnoses of the patients and targets of implantation.

Comorbid diseases were recorded in 16 (34%) patients, out of whom six had a history of epilepsy, two had a history of diabetes mellitus, three had a history of hypothyroid, three had a history of coroner artery disease, and two had chronic obstructive lung disease.

Thirty-three patients (70.2%) had no adverse effects related to DBS. Surgical-related adverse effects were observed in five patients while hardware-related adverse effects were recorded in nine (19.1%). Intraoperative period adverse effects were found in only one patient while adverse effects at the early postoperative stage were detected in six (14.2%) patients: five of them surgery-related, the other hardware-related. All long-lasting adverse effects were hardware related and recorded in eight (19%) patients. All surgical and hardware-related adverse effects of the patients were summarised in Table II.

**Surgical-Related Adverse Effects**

**Cerebral Hemorrhage**

One 60-year-old-female patient with dystonia had symptomatic ICH which resulted in death. The patient had a history of using a new oral anticoagulation drug because of atrial fibrillation, which was discontinued three days before the surgery. On the day after the surgery, the patient started to use the new oral anticoagulant without the knowledge of the clinician. Her CT scan on postoperative day one revealed no bleeding (Figure 1A). Two days after surgery, she developed a generalised epileptic seizure first and then went into a coma. Her CT depicted a bilateral hemorrhage around the electrode (Figure 1B). She subsequently underwent surgery for hematoma evacuation and decompression. However, she died due to high intracranial pressure.

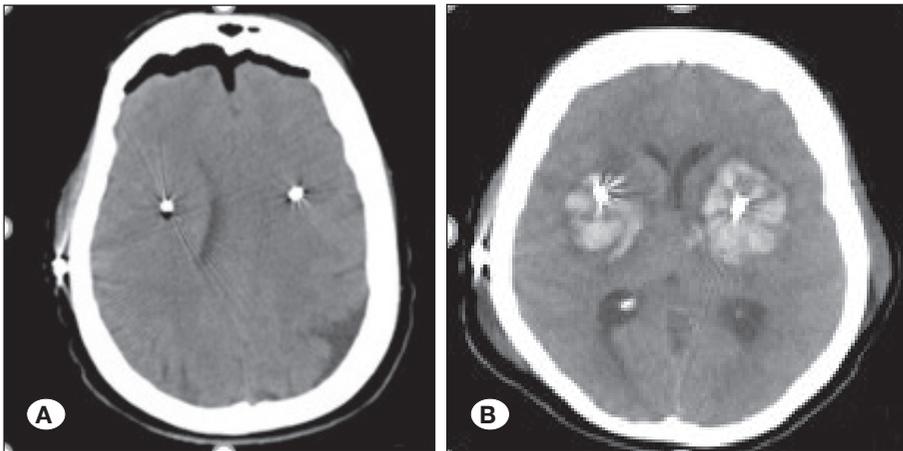
Asymptomatic ICH was observed in one patient with dystonia, a 15-year-old male, who had a small hemorrhage around the unilateral electrode on the postoperative control CT.

Another patient, a 67-year-old male with no history of epileptic seizures, developed an epileptic seizure when macro stimulation was performed to evaluate the last electrode intraoperatively. His epileptic seizure discontinued with midazolam, after which the DBS electrode was implanted in the target location with MER. CT was performed immediately after the surgery was completed. His first postoperative CT revealed pneumocephalus (Figure 2A). He had no new or worsening symptoms upon neurologic examination after the surgery and control CT scans were performed to check for any increase in the pneumocephalus. He was discharged with a baseline neurological examination and stable control CT scans. Three weeks after the DBS surgery, to check for pneumocephalus, CT was performed again and showed a bilateral subdural hematoma (Figure 2B). There was no sign of ventricular compression on the CT scan. He had no new or worsening findings on neurological examination and control CT scans over the following three weeks. However, at the end of three weeks, this subdural hematoma increased and was surgically evacuated with burr holes. The CT scan after

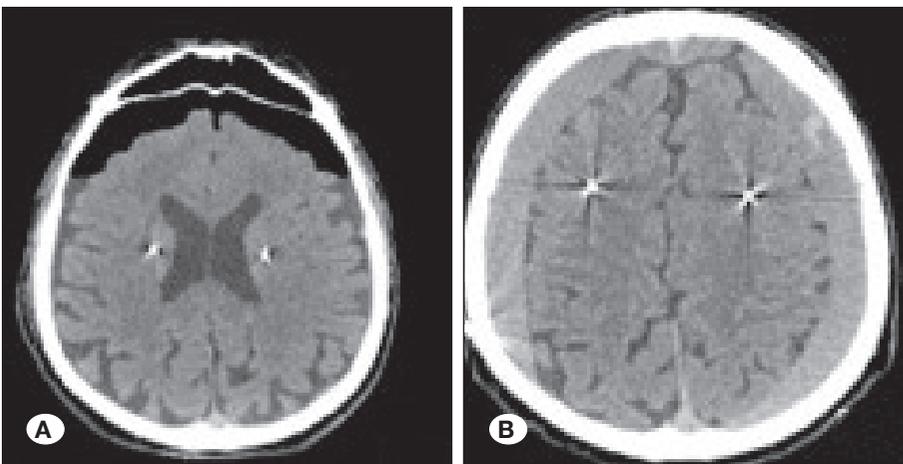
subdural hematoma evacuation did not exhibit any change in the electrodes' location from the target point.

**Non-Infectious Peri-Electrode Edema**

The first case, a 75-year-old male with ET, underwent implantation of a bilateral VIM-DBS electrode. A postoperative CT scan depicted no abnormalities and the patient was discharged with a baseline neurological examination. He presented to the emergency department two weeks after the DBS surgery with focal motor status epilepticus, which was characterized by the repetitive tonic-clonic activity of the left arm and face without alteration of mental function. After treatment of 10 mg diazepam, his epileptic seizure was discontinued and his neurological examination revealed no focal neurological deficits. His CT revealed a subtle hypodensity around the right DBS electrode near the entry site. A gadolinium-enhanced MRI was taken to evaluate the different etiologies of seizure and rule out the other reasons such as infection or infarction. This presented a wide abnormal T1 hypointense, T2 hyperintense area in the white matter in the electrode tracing in the right frontal lobe without contrast enhancement and diffusion restriction (Figure 3). He was discharged with an anti-epileptic drug and instructed to take low-dose oral steroids for a short period. A control CT scan



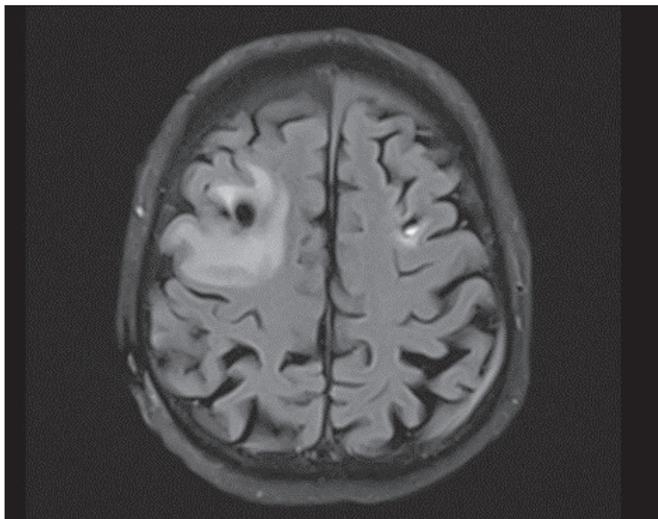
**Figure 1: A)** Axial CT scan slice showing no bleeding. **B)** Two days after surgery, an axial CT scan slices showing bilateral hemorrhage around the electrode.



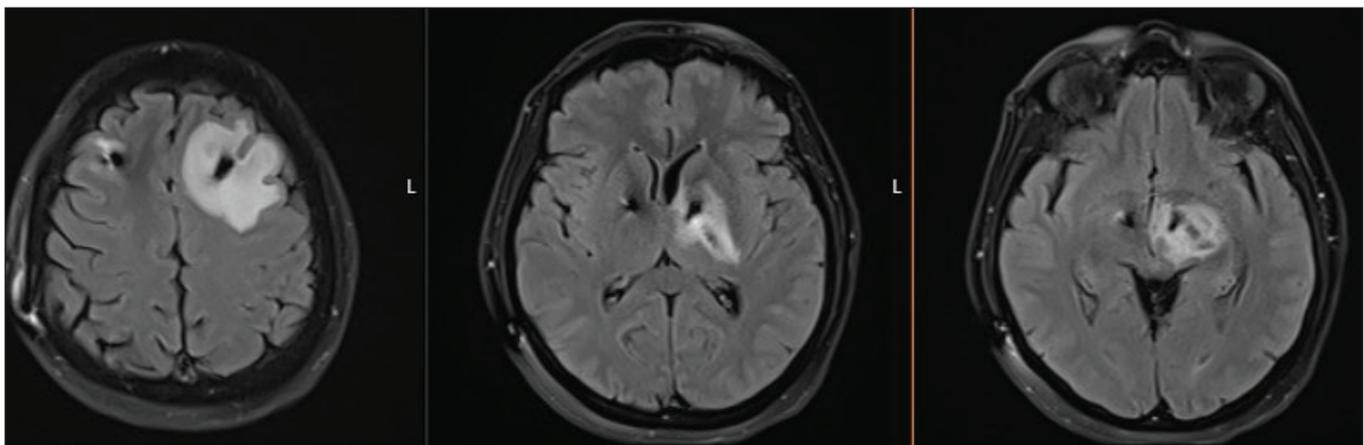
**Figure 2: A)** An axial CT scan slice presenting pneumocephalus in the bilateral frontal area. **B)** An axial CT scan slice showing bilateral chronic subdural hemorrhage.

one week later confirmed the decreased edema around the DBS electrode. He had no recurrent epileptic seizures and the anti-epileptic drug was discontinued.

The second case, a 54-year-old female with PD, underwent implantation of a bilateral STN-DBS electrode. The patient was discharged three days after surgery with a baseline neurological examination. Five days after the surgery, she presented to the emergency department complaining of a weakness in her left arm and leg, hallucinations, and confusion. On neurological examination, it was found that she had left central facial paralysis, left side hemiparesis, and right eye ptosis. Her MR showed T2 FLAIR hyperintensity in the left frontal lobe, the left lentiform nucleus, capsular interna, and left section of the mesencephalon without contrast enhancement (Figure 4). She had no signs or symptoms of infection and was treated for a short time with low-dose oral steroids. Her clinical symptoms improved within a few days.



**Figure 3:** T2 Flair MRI showing large edema surrounding the right electrode.



**Figure 4:** T2 Flair MRI depicting hyperintensity in the left frontal lobe, the left lentiform nucleus, capsular interna, and left section of the mesencephalon.

## Hardware-Related Adverse Effects

### Infection

The most prevalent hardware-related adverse effect was infection, which occurred in six (12.7%) patients. All superficial and/or deep infections which required surgical procedures or were managed with antibiotic drugs were included. The median age of the patients with infections associated with hardware was 55 years and the median infection symptom onset time after surgery was five months. There was no significant difference between the patients with and without infection regarding age and sex ( $p=0.8$ ,  $p=0.3$ , respectively).

Infection during the early postoperative stage developed in only one patient -a 60-year-old-male, with PD and was managed with only intravenous antibiotics. In two patients (4.2%), IPG required removal due to recurrent infection at the IPG site and was not reimplanted. For the first case, a 44-year-old male with PD had a history of type 2 diabetes mellitus and required the removal of the IPG six months after surgery due to recurrent infections and/or erosions. In the second case, a 31-year-old male – with cerebral palsy and generalized dystonia in addition to a baclofen pump – developed recurrent infections at both the baclofen pump and IPG sites. He needed the removal of the IPG one year after surgery. Three patients (6.3%) required local surgical repair due to infection. The most frequent bacteria were *Staphylococcus aureus* and the others were *Micrococcus luteus*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Moraxella* species, and *Staphylococcus coagulase – negative* in culture results of these patients. Table III displays the demographic features, diagnosis, culture results, and management of the patients who developed infections associated with hardware.

### Erosion without infection

A skin erosion without infection was observed in the site around IPG of a patient, a 60-year-old male with PD, 19 months after surgery. The other skin erosion without infection occurred in the burr hole side of a patient, a 62-year-old female, due to trauma. Surgical repair was performed on both patients.

**Table III:** Demographic Features, Culture Results and Management of the Patients Who Developed Hardware-Related Infection

Patient	Age, (years)	Comorbid conditions	Disease	Target	Symptom Onset of infection (Months)	Management	Culture results
1	27	Cerebral palsy	Dystonia	Bil GPI	2	Removal of system	Micrococcus luteus, Pseudomonas aeruginosa
2	44	Diabetes mellitus	PD	Bil STN	2	Removal of system	S. aureus, Citrobacter freundii
3	63	No	PD	Bil STN	10	Ab treatment, surgical repair	no
4	41	No	PD	Bil STN	2	Ab treatment, surgical repair	S. aureus
5	64	No	PD	Bil STN	12	Ab treatment, surgical repair	Moraxella species, S. aureus
6	60	No	PD	Bil STN	1	Ab treatment	Staphylococcus coag negative

**Ab treatment:** Antibiotic treatment, **Bil STN:** Bilateral subthalamic nucleus, **Bil GPI:** Bilateral globus pallidus interna, **PD:** Parkinson's disease.

### Electrode Malposition and Lead Fracture

A patient - a 60-year-old male- with PD, underwent bilateral STN-DBS implantation, following which his postoperative CT and preoperative MR imaging fusion depicted left electrode malposition. During revision surgery for the malposed electrode, lead fracture occurred as a complication. Then the third operation was performed to revise the lead fracture.

## DISCUSSION

In the present study, we evaluated the frequency and risk factors of surgery- and hardware-related adverse effects of DBS in our center. In our series, most (70.2%) of the patients had no surgery-related and/or hardware-related adverse effects. Unfortunately, one serious complication that caused mortality was observed. In the present study, the infection was the most prevalent DBS-related adverse effect. Two patients (4.2%) had very severe recurrent infections which were cured by removing the hardware system. In the literature, previous studies stated a very different prevalence of infections related to DBS ranging from 0% to 15.2% in patients who underwent the surgery (1,4,5,7,14,33,36,40,41). These varying hardware-related infection frequencies may depend on the variability of infection definitions and criteria, surgical techniques, use of prophylactic antibiotics in the perioperative and postoperative period, the follow-up period, and the number of patients in the studies. In some studies, the prevalence of hardware-related infection is calculated solely by the number of patients, while others are calculated by the number of surgical procedures. In the extant literature, some have included all superficial and/or deep infections related to hardware (4,5,7,14,36) whereas others have included only hardware-related deep infections which required surgical repair (31,37,40). Sillay et al. reported a 4.5% incidence of hardware-related infections requiring further surgery in a large series of patients who underwent DBS

surgery (40). Piacentino et al. reported an 8.5% prevalence of hardware-related deep infections requiring further surgery (37).

In our institution, every patient received intravenous cefuroxime intraoperatively and continued to use antibiotics during the week after surgery. We reviewed the studies investigating the risk and treatment of infections related to hardware. Bhatia et al. found that the use of vancomycin and bag-attached gentamicin instead of cefuroxime for antibiotic prophylaxis did not significantly reduce the proportion of hardware-related infections (4). Miller et al. have reported that the combination of the injection of a local solution containing neomycin and polymyxin into the surgical wound and intravenous (cefazolin 1–2 g) or vancomycin (1 g) antibiotic therapy may reduce the rates of hardware-related deep infections (31). Hamani et al. reviewed the literature, including ten studies, and found a mean hardware-related infection rate of 6.1% (22), stating that most DBS-related infections were managed by hardware removal. Similarly, we had removed hardware because of resistant infections in two of our cases.

In the present study, erosion without infection which required further surgical repair was observed in two patients (4.2%). Additionally, we recorded one lead fracture case in this study. Jitkriksadaku et al. systematically reviewed 96 articles to conclude that the frequencies of lead fracture and skin erosions without infections were 1.5% and 0.48% respectively (25).

We recorded one serious symptomatic ICH (2% per patient) and one asymptomatic ICH (1.1% per electrode). We believe that this serious ICH developed due to the patient's use of new oral anticoagulation drugs in the early postoperative period without the knowledge of the clinician. In the literature, the prevalence of DBS-related ICH ranged from 0.6% to

3.5% per electrode (3,6,20,30,39,44). A previous study with a large number of case series reported that the frequency of symptomatic ICH and asymptomatic ICH was 1.1% and 0.5% per patient respectively (15). Another recent study revealed that the frequency of ICH after DBS surgery was 4.7% per patient (35). According to a few studies, the majority of ICH complications are preventable with meticulous stereotactic planning to evade blood vessel by high-resolution MRI (28, 32, 35). Many studies have reported that MER may be associated with an increased risk of intracerebral hemorrhage (6,7,30,36,37). However, a study reported that the risk of hemorrhagic complications due to MER was very low (3). In our series, we preferred two or three microelectrode insertions to avoid this complication. Planning the electrode trajectory very carefully, avoiding the sulcus, blood vessel, and ventricles, and performing high-resolution MR with contrast agent in all patients are extremely important points at this stage. In our series, the rates of symptomatic and asymptomatic DBS-related ICH were not higher than in the literature. A chronic subdural hematoma in one patient was recorded one month after the placement of bilateral STN-DBS. The frequency of subdural hemorrhage ranged from 0.3% to 1.8% per patient in the literature (3,6,19,26,34,43).

We recorded one (2.1%) intraoperative epileptic seizure in the present study. In the literature, the occurrence of epileptic seizures during DBS surgery ranged from 0.9% to 2.3% in patients (3,10,19,26,43). Six (12.7%) of our patients had a history of epilepsy before the surgery and they had no seizures during surgery or increased seizure frequency in the postoperative period.

In the present study, we observed unilateral non-infectious peri-electrode edema in around two of 90 DBS electrodes (2.2%) which occurred in the early postoperative period, causing transient neurological symptoms. The prevalence of peri-electrode edema after DBS surgery without infection and infarction ranged from 0.04% to 39% in the literature (2,11-13,16,17,24,27,29,38). Peri-electrode edema can be observed as a symptomatic complication (2,11,12,16,18,24,27,29) or can be found during routine imaging in asymptomatic patients (13,17,38). Fenoy et al. presented a 2.1 % incidence of peri-lead edema which caused acute clinical neurological presentations per electrode (16). Moreover, Ryu et al. have shown that 39% of patients had asymptomatic transient MRI signal changes within three months of DBS implantation (38). Englot et al. reviewed postoperative MR imaging of 133 patients who underwent DBS surgery and found a 6.3% frequency of abnormal T2 signal hyperintensity around the DBS lead per electrode. They also observed that only 26% of peri-lead edema caused clinical neurological symptoms (13). Borrellini et al. evaluated brain MRI of 19 patients between seven and 20 days after DBS surgery and found that MRI showed peri-lead edema in all patients. They concluded that peri-electrode edema during the first seven to 60 days after DBS surgery is a prevalent, transient reaction and may not require treatment with corticosteroids (9). However, other studies recommended steroid therapy for the management of peri-lead edema (12,13,16). The pathophysiology of peri-lead edema also remains. Some authors have considered

that a highly possible mechanism causing peri-lead edema is an immune reaction such as hypersensitivity and an allergic reaction to the surgery and/or to the DBS electrode (11,13,38). Post-mortem analysis of the patients who underwent DBS surgery within three months before death presented little tissue damage and a mild inflammatory reaction around the electrodes (23). However, Kim et al. have concluded that a mechanical breakdown of the blood-brain barrier during MER recordings may be a reason for the peri-lead edema (27). We think that there is still no consensus for the pathophysiology and management of peri-lead edema.

## ■ CONCLUSION

Several adverse effects of DBS surgery were observed in the early postoperative stage and longer periods, although no adverse effects were found in most patients. The patients should be informed about all possible adverse effects of DBS surgery and they were closely followed up during each period. Furthermore, we believe that the clinician should always be careful about early detection and management of the adverse effects of DBS surgery.

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## ■ AUTHORSHIP CONTRIBUTION

**Study conception and design:** NSE, HC, TU

**Data collection:** NSE, TU

**Analysis and interpretation of results:** NSE, HC, SSO

**Draft manuscript preparation:** NSE, HC

**Critical revision of the article:** NSE, TU, HC

**Other (study supervision, fundings, materials, etc...):** NSE, TU

All authors (NSE, SSO, HC, TU) reviewed the results and approved the final version of the manuscript.

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