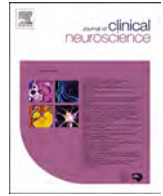


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Original Research

## Delayed-onset seizures after subthalamic nucleus deep brain stimulation surgery for Parkinson's disease

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## ABSTRACT

**Background:** Delayed-onset seizures after deep brain stimulation (DBS) surgery were seldom reported. This study summarized the clinical characteristics of delayed-onset seizures after subthalamic nucleus (STN) DBS surgery for Parkinson's disease (PD) and analyzed risk factors.**Methods:** A single-center retrospective study containing consecutive STN-DBS PD patients from 2006 to 2021 was performed. Seizures occurred during the DBS surgery or within one month after DBS surgery were identified based on routine clinical records. Patients with postoperative magnetic resonance imaging (MRI) were included to further analyze the risk factors for postoperative seizures with univariate and multivariate statistical methods.**Results:** 341 consecutive PD patients treated with bilateral STN-DBS surgery were identified, and five patients experienced seizures after DBS surgery with an incidence of 1.47%. All seizures of the five cases were characterized as delayed onset with average 12 days post-operatively. All seizures presented as generalized tonic-clonic seizures and didn't recur after the first onset. In those seizures cases, peri-electrode edema was found in both hemispheres without hemorrhage and infarction. The average diameter of peri-electrode edema of patients with seizures was larger than those without seizures ( $3.15 \pm 1.00$  cm vs  $1.57 \pm 1.02$  cm,  $p = 0.005$ ). Multivariate risk factor analysis indicated that seizures were only associated with the diameter of peri-electrode edema (OR 4.144, 95% CI 1.269–13.530,  $p = 0.019$ ).**Conclusions:** Delayed-onset seizures after STN-DBS surgery in PD patients were uncommon with an incidence of 1.47% in this study. The seizures were transient and self-limiting, with no developing into chronic epilepsy. Peri-electrode edema was a risk factor for delayed-onset seizures after DBS surgery. Patients with an average peri-electrode edema diameter  $> 2.70$  cm had a higher risk to develop seizures.

## 1. Introduction

Deep brain stimulation (DBS) is a well-established surgical therapy for some movement and psychiatric disorders. Patients are exposed in risks of trauma and implanted simulator damage when seizures occur, though seizures are not common postoperative adverse event of deep brain stimulation surgery. Previous studies indicated that the risk factors for seizures related to DBS included hemorrhage, peri-electrode edema,

and increased age [1–3]. Most of the seizures occurred during electrode implantation procedures or within 48 h after DBS surgery [1–3], and delayed-onset seizures were seldom reported. However, this seizures incidence time-point presents quite different from those reports when retrospectively screening those PD patients who underwent subthalamic nucleus (STN) DBS in our center. We found that the seizures after DBS surgery were mainly delayed-onset (1–2 weeks after surgery). Therefore, this study summarized the clinical characteristics of delayed-onset

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seizures after DBS surgery and analyzed related risk factors.

## 2. Materials and methods

### 2.1. Study design and data collection

341 consecutive PD patients received bilateral STN-DBS surgery in the First Affiliated Hospital of Sun Yat-sen University from 2006 to 2021. All patients' clinical data were recorded and collected. Implantable pulse generator (IPG) was regularly turned on for programming after one month of DBS surgery. Seizures occurred during DBS surgery or within one month after DBS surgery were identified for the study. The occurrence of seizures was extracted from routine clinical records. To further explore the risk factors of postoperative seizures, postoperative neuroimages were reviewed. 109 patients without postoperative magnetic resonance imaging (MRI) were excluded, and 202 patients were included in further risk factors analysis (Fig. 1).

### 2.2. DBS surgical procedure

All patients underwent 3.0-T MRI scans before surgery. The anti-parkinsonian medications were withdrawn 12 h before surgery. On the surgery day, each patient was positioned in a stereotactic frame (Leksell Coordinate Frame G, Elekta, Stockholm, Sweden) using local anesthesia, and then received computed tomography (CT) scan. The stereotactic CT images were merged with the non-stereotactic MRI images in for surgical planning. Bilateral STNs were selected as targets for all patients.

The surgeries were performed under general anesthesia or local anesthesia. A single-track microelectrode recording (MER) strategy was applied to identify the targets for all patients. An arc-shaped scalp incision and a burr hole were made. The microelectrode was implanted to record the neurophysiological signals. Detail MER procedure could be found in our previous report [4]. After satisfactory STN signal was obtained, the permanent electrode was implanted. Another electrode was implanted following the same procedure. IPG was next implanted under

general anesthesia. All patients received intravenous continuous infusion of sodium valproate during the *peri*-DBS surgery and within 24–48 h after the surgery. Intravenous anti-epilepsy drug was then adjusted into oral sodium valproate or levetiracetam at 3rd day after DBS surgery for at least 2 weeks. More detailed surgical steps could be referred in our team's previous published articles [5–8].

### 2.3. Postoperative radiographic measurement

202 patients received postoperative 1.5-T MRI to verify the electrode location at postoperative 4 to 7 days. Peri-electrode edema was defined as the signal hyperintensity surrounding the implanted electrodes on T2-weighted images, but the hyperintensity less than twice the diameter of the electrode was excluded as artifact [9]. The diameter of *peri*-electrode edema and the distance from the electrode punctured point in the cortex to the precentral gyrus (PreCG) were assessed. The diameter of *peri*-electrode edema was measured as the diameter of the maximum edema region around the electrode in axial view in the cortex [8]. Average of the major diameter and minor diameter was defined as diameter (Fig. 2A) with *peri*-electrode edema region not showing circular. The distance from the electrode punctured point in the cortex to PreCG was accessed as the shortest vertical distance to the line of central anterior sulcus in axial view at the level of the electrode cortical punctured point (Fig. 2B). Both two parameters above were measured in both hemispheres. The average value of the left and right hemispheres was calculated and applied for analysis.

### 2.4. Statistical analysis

A descriptive analysis was used to summarize patients' baseline characteristics. The quantitative data presented as mean  $\pm$  standard deviation (SD), and the qualitative data presented as number of cases and percentages. An unpaired Mann-Whitney *U* test was applied to detect significant differences for continuous variables. A Fisher's exact test or a Yates' correction for continuity was used to compare categorical variables. A receiver operating characteristic (ROC) curve analysis was

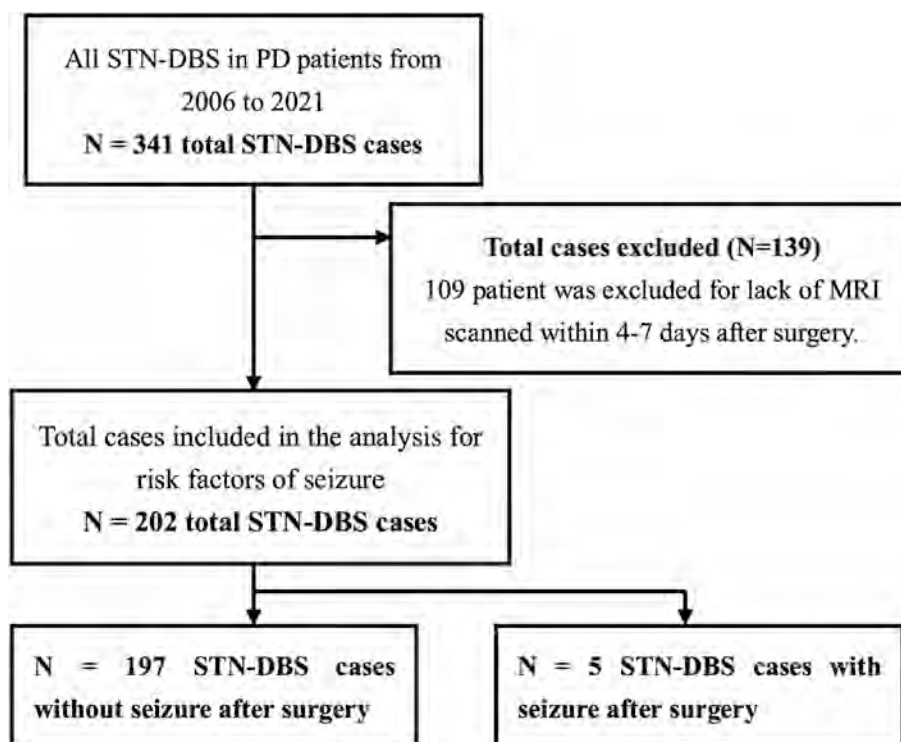
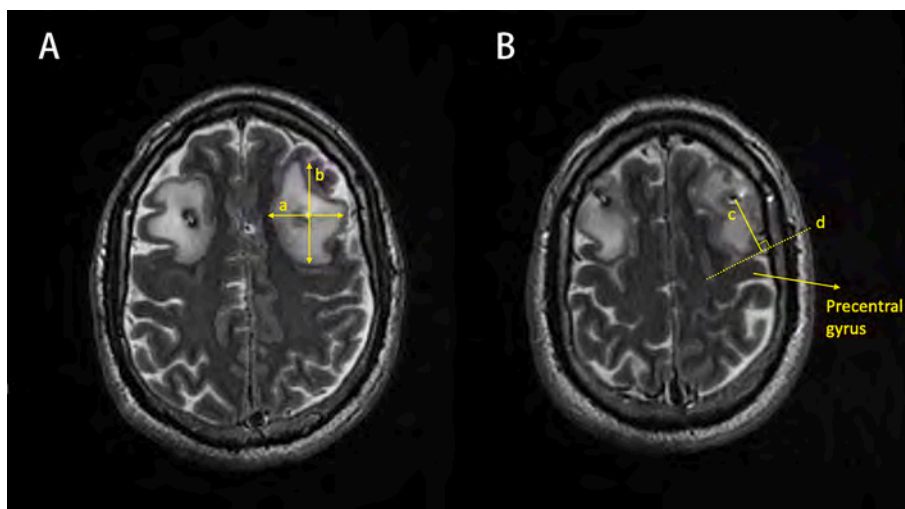


Fig. 1. Study population and diagram.



**Fig. 2.** Postoperative radiographic measurement. (A) The diameter of *peri*-electrode edema was calculated as the average of the minor diameter (length of the yellow line with double arrows of a) and the major diameter (length of the yellow line of b) of the edema region. (B) The distance from electrode punctured point in cortex to precentral gyrus was measured as the length of the perpendicular (the yellow line of c) with shortest distance from the electrode to the imaginary anatomical line of central anterior sulcus (the yellow dotted line d).

performed to identify the cut-off point of *peri*-electrode edema diameter. A binary multivariate logistic regression was performed for analyzing seizures’ risk factors, with the odds ratio (OR) and the 95 % confidence interval (CI) of the risk factors calculated. The threshold level of significance for all analyses was set at  $p \leq 0.05$ . The statistical analysis was performed using SPSS Statistics (version 25.0; IBM Corp, Armonk, NY).

### 3. Results

#### 3.1. Clinical characteristics of postoperative seizures

Of total 341 patients who underwent bilateral STN-DBS surgery between 2006 and 2021, five patients experienced seizures after DBS surgery with incidence of 1.47 %. All 5 patients were included within the 202 patients with intact postoperative MRI in the further analysis of the risk factors of postoperative seizures. The patients’ demographic and clinical characteristics were summarized in Table 1.

The seizures of five patients were characterized as delayed onset with an average onset time of postoperative 12 days (ranging from 7 to 14 days) (Table 2). Four patients (patients 2 to 5 in Table 2) experienced a single seizure after discharge and then were sent back to the emergency department of hospital. One patient (patient 1 in Table 2) experienced seizures three times in one day, who also suffered for refractory hyponatremia (120–125 mmol/L of serum sodium) after DBS surgery during hospitalized period. None of other patients in this series experienced refractory hyponatremia. All seizures presented as generalized tonic-clonic seizures. The simulators had not yet been turned on for all cases when the seizures occurred. All 5 patients didn’t present epileptic past-history before DBS surgery. All 5 patients were still taking antiepileptic drugs when the seizures occurred. *Peri*-electrode edema was found in both hemispheres in all cases after reviewing their routine postoperative MRI (before seizure occurrence). The edema regions were extensive and close to the precentral gyrus in four patients (Fig. 3). None of those 5 patients presented any clinical symptoms, neurologic signs or image abnormalities at postoperative CT and MRI scan timepoint. Patients received immediate intravenous antiepileptic treatment and dehydration therapy when seizure occurred. All 5 case were free of seizures at 1 year follow-up.

MER, microelectrode recordings; PreCG, precentral gyrus; F, female; M, male; AEDs, Antiepileptic drugs.

**Table 1**

Comparison of clinical characteristics between two group patients after DBS surgery.

Variable	With seizure (n = 5)	Without seizure (n = 197)	P value
Sex			1.000 <sup>a</sup>
Male	3 (60.00 %)	117 (59.39 %)	
Female	2 (40.00 %)	80 (40.61 %)	
Age (y)	55.80 ± 6.46	60.03 ± 9.34	0.185 <sup>b</sup>
Duration of PD (yrs)	7.90 ± 2.45	9.71 ± 3.92	0.294 <sup>b</sup>
Length of surgery (min)	386.20 ± 77.96	369.65 ± 66.54	0.422 <sup>b</sup>
MER passages	2.40 ± 0.89	2.69 ± 1.08	0.481 <sup>b</sup>
Pneumocephalus volume (cm <sup>3</sup> )	7.44 ± 15.42	12.36 ± 14.53	0.098 <sup>b</sup>
Anesthesia methods			0.029 <sup>c</sup>
Local anesthesia	2 (40.00 %)	10 (5.10 %)	
General anesthesia	3 (60.00 %)	187 (95.10 %)	
Diameter of <i>peri</i> -electrode edema (cm)			
Left side	3.28 ± 1.01	1.57 ± 1.13	0.005 <sup>b*</sup>
Right side	3.02 ± 1.21	1.57 ± 1.19	0.023 <sup>b*</sup>
Average	3.15 ± 1.00	1.57 ± 1.02	0.005 <sup>b*</sup>
Distance of electrode to PreCG (cm)			
Left side	2.41 ± 0.46	2.73 ± 0.56	0.180 <sup>b</sup>
Right side	2.38 ± 0.24	2.68 ± 0.59	0.161 <sup>b</sup>
Average	2.39 ± 0.34	2.71 ± 0.50	0.128 <sup>b</sup>
Postoperative hemorrhage	0 (0.00 %)	1 (0.51 %)	0.975 <sup>c</sup>

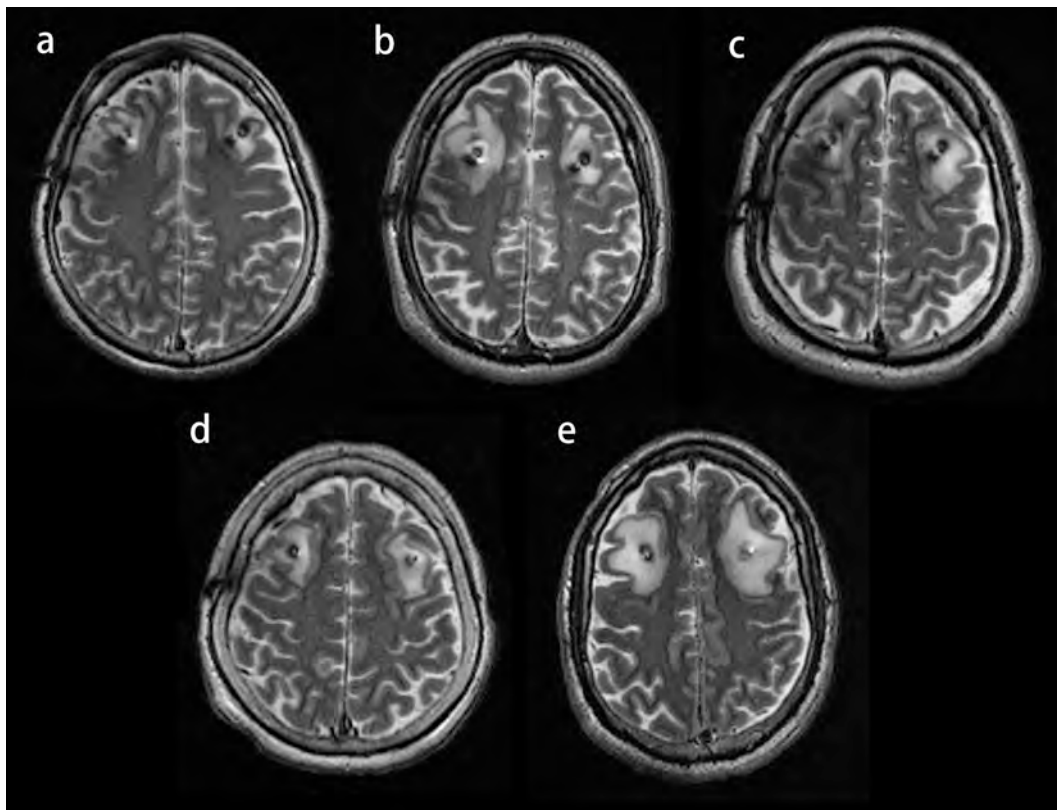
\* Statistically significant at  $P < 0.05$ . a Yates’ correction for continuity. b Mann-Whitney *U* test. c Fisher’s exact test. PD, Parkinson’s disease; MER, microelectrode recordings; PreCG, precentral gyrus.

#### 3.2. Postoperative delayed-onset seizures and *peri*-electrode edema

The average diameter of seizure patients’ *peri*-electrode edema was larger than the no seizures group with statistical significance ( $3.15 \pm 1.00$  cm vs  $1.57 \pm 1.02$  cm,  $p = 0.005$ , unpaired Mann-Whitney *U* test). The average distance from the electrode punctured point in the cortex to PreCG of seizure patients was smaller than the no seizures group. However, no statistical significance was found ( $2.39 \pm 0.34$  cm vs  $2.70 \pm 0.50$  cm,  $p = 0.128$ , unpaired Mann-Whitney *U* test). The average diameter of *peri*-electrode edema for all 202 patients was  $1.61 \pm 1.05$  cm (Fig. 4). ROC curve analysis was performed to determine the threshold that raised suspicion of future seizures in these patients. The result

**Table 2**  
Characteristics of patients with delay-onset seizures after DBS surgery.

Case	Age (yrs)	Sex	Anesthesia methods	MER passages	Diameter of <i>peri</i> -electrode edema (cm)		Distance from electrode to PreCG (cm)		MRI scanned (days postop)	Seizures onset (days postop)	Times of seizures	Treatment
					Left	Right	Left	Right				
1	55	F	General	4	1.88	1.70	3.02	2.74	4	13	3	AEDs
2	55	M	General	2	3.25	4.54	2.14	2.26	5	14	1	AEDs, steroids
3	46	M	Local	2	3.37	2.04	2.34	2.17	5	7	1	AEDs, steroids
4	63	F	General	2	3.14	2.88	1.84	2.22	5	13	1	AEDs, steroids
5	60	M	Local	2	4.74	3.92	2.7	2.5	5	13	1	AEDs, steroids



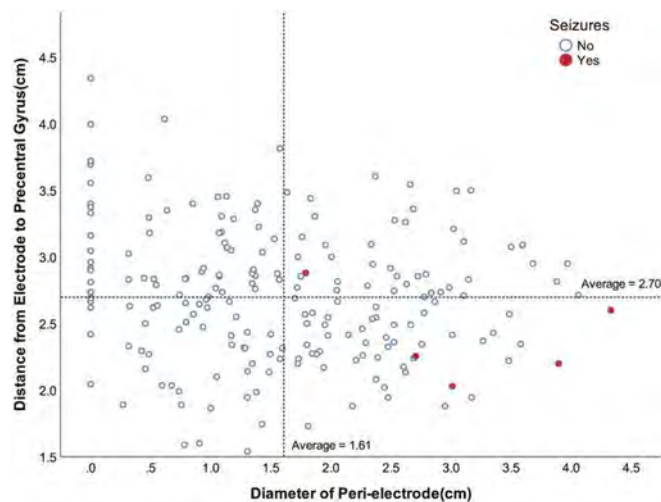
**Fig. 3.** Postoperative *peri*-electrode edema on MRI of the five seizures patients. The figures of a-e presented the *peri*-electrode edema regions of the five patients (No. 1 to 5 in Table 2) respectively. The diameter of the *peri*-electrode edema: (a) left 1.88 cm, right 1.70 cm; (b) left 3.25 cm, right 4.54 cm; (c) left 3.37 cm, right 2.04 cm, (d) left 3.14 cm, right 2.88 cm; (e) left 4.74 cm, right 3.92 cm.

indicated that patients with an average *peri*-electrode edema diameter > 2.70 cm had a higher possibility to develop seizures with the best sensitivity and specificity (sensitivity of 0.800, specificity of 0.853, a positive predictive value of 0.121, a negative predictive value of 0.994, and area under curve of 0.869,  $p = 0.005$ , ROC curve analysis). In this series, 12.1 % of the patients (4/33) with an average edema diameter > 2.70 cm developed seizures postoperatively, and only 0.50 % of patients (1/169) with an average edema diameter  $\leq$  2.70 cm developed seizures ( $p = 0.003$ , Fisher's exact test).

### 3.3. Univariate and multivariate analysis of risk factors for delayed-onset seizures

There was no difference in sex, age, duration of PD, length of surgery time, MER passage number, postoperative pneumocephalus volume, and incidence of postoperative hemorrhage between patients with and

without postoperative seizures (Table 1). No *trans*-ventricular trajectory was found for all patients. Two (40.00 %) of the five patients with seizures underwent electrode implantation under local anesthesia. 10 (5.10 %) of the 197 patients without seizures underwent procedures under local anesthesia, which was statistically different ( $p = 0.029$ , Fisher's exact test). Thus, *peri*-electrode edema and anesthesia methods (local anesthesia) were associated with delayed-onset seizures after DBS surgery in univariate analysis. These two factors were included in further binary multivariate logistic regression (enter method), and the results indicated that seizures were associated with the diameter of *peri*-electrode edema (OR 4.144, 95 % CI 1.269–13.530,  $p = 0.019$ ), but not anesthesia methods (local anesthesia compared to general anesthesia, OR 3.428, 95 % CI 0.380–30.967,  $p = 0.273$ ).



**Fig. 4.** The scatterplot to depict the distributions of *peri*-electrode edema diameter and distance from electrode to precentral gyrus of all patients. The red filled circles represent the patients with seizures. The blue unfilled circles represent the patients without seizures. The vertical dotted line represents the average diameter of *peri*-electrode edema of 1.61 cm, and the horizontal dotted line represents the average distance from electrode to precentral gyrus of 2.70 cm.

#### 4. Discussion

In this study, we reviewed a case series of PD patients who underwent STN-DBS surgery. The incidence of postoperative seizures was 1.47 %, with no intraoperative seizures. All DBS related seizures in this study were delayed onset of postoperative 1–2 weeks. Further analysis indicated that *peri*-electrode edema was a risk factor for the delayed-onset seizures. Patients with an average *peri*-electrode edema diameter > 2.70 cm had a higher possibility to develop postoperative seizures.

Seizures associated with DBS can be classified as procedural related seizures and epilepsy following chronic DBS [1,10]. In this study, all delayed-onset seizures were procedural-related seizures, as the IPG had not yet been turned on. The incidence of postoperative procedural related seizures in this study is similar with previous studies. Coley et al. reported that the incidence of seizures following DBS electrode implantation was around 2.7 %. Pouratian et al. reported an incidence of 4.3 % (7 of 161) for postoperative DBS seizures in PD patients, which were all generalized tonic-clonic seizures [2]. Bakay et al. reported that 1.06 % (4 of 378) patients undergoing DBS surgery experienced postoperative seizures [11].

The onset time of procedural related seizures may vary from electrode implantation to postoperative several weeks. All postoperative seizures in our case series were delayed onset, which occurred within 1–2 weeks after surgery with an average time of 12 days. While previous reports showed most seizures occurred intraoperatively or within 1–2 days after surgery. Coley et al. reported that at least 75 % of seizures occurred around electrode implantation time-point and many of them accompanied with intracranial hemorrhage. Patients without a specified periprocedural or immediate postoperative seizure were defined as delayed seizure, with incidence around 0.5 % [1]. Among 7 cases seizures reported by Pouratian et al., Five (71 %) of them occurred within 24 h of surgery and one occurred within 24–48 h after surgery [2]. Atchley et al. also reported that 14 (63.6 %) of 22 cases postoperative seizures occurred less than 24 h after electrode placement (median postoperative day 1, interquartile range 0–3 days, mean  $2.8 \pm 4.9$  days) [3]. Therefore, our study suggests that the onset of seizures associated with DBS surgery are not limited to the perioperative period. The patients are still exposed in seizures risk even after discharge from hospital,

though the incidence is relatively low (1.47 %).

In this study, results indicated that delayed-onset seizures were associated with extensive *peri*-electrode edema. Previous studies reported that symptomatic edema associated with electrode implantation in DBS surgery could present with seizures [12–15]. *Peri*-electrode edema was not a rare complication of DBS surgery. Only a few developed as symptomatic edema. A meta-analysis study indicated that the incidence of *peri*-electrode edema was 35.8 %, while the incidence of symptomatic *peri*-electrode edema was only 3.1 % [16]. The CT imaging scan time of identifying edema varied from 1 day to 2 months after surgery [16,17]. In our study, we found that 78.22 % (316 of 404) implanted electrodes presented with *peri*-electrode edema. The recognition of edema was identified via routine MRI scan at 4–7 days after lead implantation in our center. *Peri*-electrode edema seemed to be more common for DBS surgery in our study. Reason might be that MRI was more sensitive to recognize the edema regions compared with CT as reported.

As for risk factor of seizure, no robust conclusions could be drawn for the inevitable bias of retrospective study. In our study, we found the diameter of *peri*-electrode edema and anesthesia methods were associated with delayed-onset seizures in univariate analysis, while only edema was significant in the multivariate model. Pouratian et al. identified 3 significant associations for postoperative seizures: abnormal findings on postoperative imaging (hemorrhage, edema, and or ischemia), age greater than 60 years, and *trans*-ventricular electrode trajectories in univariate analysis. But only abnormal findings on postoperative imaging was significant factor identified on multivariate analysis [2]. Johnson et al. reported that multiple sclerosis was a risk factor for postoperative seizures [18]. However, most of the seizures in previous reports occurred within 48 h of DBS surgery, which were different from our study. Thus, the risk factors analysis may be not comparable.

Seizures originate from abnormal neuronal activity in the cortex. The increase of blood–brain barrier permeability in cerebral edema may accelerate seizure activity [19]. Thus, patients with extensive *peri*-electrode edema are more sensitive to postoperative seizures. In this study, all seizure patients presented with generalized tonic-clonic seizures. Four (patients 2 to 5 in Table 2) of the five patients with postoperative seizures in this study had extensive *peri*-electrode edema nearby the PreCG. However, the other one patient (patient 1 in Table 2) had an average diameter of edema regions which were not close to PreCG. This patient (case 1) was still hospitalized for refractory hyponatremia after DBS surgery when the seizure occurred. This patient (case 1) developed hyponatremia at 10 days postoperatively and reached the lowest level of serum sodium of 120 mmol/L at seizure onset day. Reports found that patients with lower serum sodium had higher risk of seizures [20,21]. We assumed that for this patient, postoperative refractory hyponatremia was the primary causation of the seizures.

Antiepileptic prophylaxis was applied intraoperatively and postoperatively for all patients who underwent DBS surgery including those who developed delay-onset seizures. Pouratian et al. reported that patients combined with ischemia, edema, or hemorrhage on postoperative imaging were prescribed a 1-week course of anticonvulsant therapy [2]. Bakay et al. recommended that antiepileptic prophylaxis was not necessary for the low incidence (1.06 %) of seizures [11]. Prospective studies are needed to investigate whether antiepileptic prophylaxis should be applied for DBS surgery. For the seizures cases with edema in the study of Deogaonkar et al., steroids and antiepileptic drugs were prescribed [12]. In our study, all patients received immediate intravenous sodium valproate and sedative treatment after seizure attack. Then they were prescribed oral antiepileptic drugs of sodium valproate and levetiracetam for at least 6 months. All patients were free of seizures after the first onset.

The highlight of this study is that this is the first focused report of delayed-onset seizures after DBS surgery treating PD. Further analysis indicated that postoperative *peri*-electrode edema was an obvious risk

factor, which could be used as a potential predictor of seizures. The results suggested that patients were still exposed in risk of seizures after discharge, even though showing no neurological signs in the perioperative period of hospitalization after DBS surgery. However, there were some limitations in the study. Firstly, bias is inevitably induced by its retrospective nature. Secondly, some seizure records could be lost inadvertently during the long-time span. Thirdly, the methods available for analysis the risk factors were limited by the nature of the retrospective single-center study. Further prospective and multicenter studies are needed to verify the results in future.

## 5. Conclusions

Delayed-onset seizure after STN-DBS treating PD patients was uncommon with an incidence of 1.47 %. The seizures were transient and self-limiting, not easily developing into chronic epilepsy. Peri-electrode edema was a risk factor for delayed-onset seizures after DBS surgery. Patients with an average *peri*-electrode edema diameter > 2.70 cm had a higher risk to develop seizures.

## 6. Statements and Declarations

The research project was approved by the independent ethics committee for clinical research and animal trials of the First Affiliated Hospital of Sun Yat-sen University (IIT2021-142). Patient consent was waived due to the retrospective nature of the study and that no identified feature of participating patients was involved in the study, which was approved by the local ethics committee.

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## CRedit authorship contribution statement

**Bin Wu:** Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Jinlong Liu:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization. **Lulu Jiang:** Investigation, Formal analysis. **Jiakun Xu:** Investigation, Data curation. **Ruoheng Xuan:** Investigation. **Yuting Ling:** Investigation. **Qianqian Guo:** Investigation. **Nan Jiang:** Writing – review & editing, Investigation. **Ling Chen:** Writing – review & editing, Supervision. **Changming Zhang:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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