

The safety issues and hardware-related complications of deep brain stimulation therapy: a single-center retrospective analysis of 478 patients with Parkinson's disease

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Introduction: Deep brain stimulation (DBS) is a well-established therapy for the treatment of advanced Parkinson's disease (PD) in patients experiencing motor fluctuations and medication-refractory tremor. Despite the relative tolerability and safety of this procedure, associated complications and unnatural deaths are still unavoidable.

Methods: In this study, hardware-related complications and the causes of unnatural death were retrospectively analyzed in 478 patients with PD who were treated with DBS.

Results: The results showed a 3-year survival rate of 98.6% and a 5-year survival rate of 96.4% for patients with PD who underwent DBS treatment at the study center. Pneumonia was the cause of death with the highest frequency. Prophylactic antibiotics and steroids or antihistamine drugs were adopted to reduce the risk of infection. Twenty-two patients (4.6%) experienced hardware-related complications.

Conclusion: Deaths of PD patients who receive DBS are typically unrelated to the disease itself or complications associated with the surgery. Pneumonia, malignant tumors, asphyxia, and multiple-organ failure are the common causes of death. Swallowing-related problems may be the most important clinical symptom in late-stage PD, as they cannot be stabilized or improved by DBS alone, and are potentially lethal. Although prophylactic antibiotics and steroids or antihistamine drugs may reduce the risk of infection, it is imperative to identify high-risk patients for whom a therapeutic approach not requiring an implantable device is more suitable, for example, pallidotomy and potentially transcranial ultrasound.

Keywords: motor fluctuations, tolerability, death, survival, antibiotics, steroids

Introduction

Parkinson's disease (PD) is one of the most commonly seen neurodegenerative diseases, affecting about 1% of people over 60 years old.¹ Deep brain stimulation (DBS) is an important neurosurgical intervention for patients with advanced PD who are experiencing strong tremor or motor fluctuations, and has become the most common surgical technique used in such cases.^{2,3} Despite the good tolerability and safety of this procedure, complications and unnatural deaths associated with the treatment are still unavoidable. DBS was also regarded as a more invasive procedure than pallidotomy in terms of hardware. In this study, hardware-related complications and the causes of unnatural death were retrospectively analyzed in patients with PD who were treated with DBS in Shanghai Ruijin Hospital, including a long-term follow-up, to provide reference points for the optimization of surgical techniques and equipment.

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Methods

Patients and clinical data

Patients admitted from September 1999 to December 2012, who met the inclusion criteria for DBS surgery for PD, were analyzed; all patients were operated on by the same surgeon and his team. Inclusion criteria for DBS surgery were the following: 1) age 18–75 years, and primary PD with a disease duration ≥ 5 years (according to the UK brain bank diagnostic criteria for primary PD or China primary PD diagnostic criteria); 2) treatment with the best available drugs (full dose or at least treated with L-dopa drugs) to good effect previously, but with obviously decreased efficacy at admission, or the presence of movement disorders that affect the quality of daily life; and 3) Hoehn–Yahr 2.5–4 stage during the PD-off period, with a total daily off duration ≥ 4 hours. Exclusion criteria were the following: 1) syndromic PD or Parkinson's-plus syndromes; 2) current comorbid severe cognitive impairment (Mini-Mental State Examination score for illiteracy < 17 , elementary school < 20 , middle school or above < 24), and mental or physical diseases; and 3) surgical contraindications (such as cochlear implant, cardiac defibrillator implantation history, and coagulation disorders).

A total of 515 patients with PD met the inclusion criteria. All included patients underwent unilateral or bilateral DBS electrode implantation in the subthalamic nucleus (STN; $n=477$) or globus pallidus internus ($n=38$). The mean age of onset of PD in these patients was 51.5 ± 15.3 years, and the mean age at time of surgery was 57.5 ± 11.1 years. The follow-up duration was 3–16 years. The study was approved by Ruijin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine, and for all included patients, written informed consent was provided.

Surgical procedure

Briefly, a Leksell stereotactic head frame was mounted on the patient's skull on the day of surgery under local anesthesia, and was then aligned parallel to the anterior commissure–posterior commissure line as closely as possible. A General Electric 1.5 T magnetic resonance (MR) imaging scanner was used for a positioning scan (axial and coronal T1- and T2-weighted images with 1.0 mm slice thickness and no spacing). The surgeon confirmed the coordinates of the surgical target and the angle of trajectory based on MR images. Under local anesthesia, the surgical incision was made according to the calculated target coordinates, and a hole was drilled through the skull. The target position was confirmed by electrode (3387 or 3389; Medtronic Inc., Minneapolis, MN, USA) stimulation. The implantable pulse generator

(IPG), including Soletra and Kinetra, was then implanted into the subclavian subcutaneous pouch under general anesthesia. The electrodes were connected to the IPG through an extension wire (7482-51; Medtronic, Inc). The position of the electrodes was examined again in a postoperative review, and after intracranial edema subsided, follow-up and adjustments were conducted. Electrode parameters (contact point, voltage, pulse width, and frequency) were adjusted based on the patient's condition. Further details of the surgical procedure have been described previously.^{4–6} A one-time intramuscular injection of betamethasone is administered after surgery, and ceftriaxone (or levofloxacin for allergic patients) was given for 3 days after surgery as a prophylactic.

Postoperative follow-up

Follow-up analysis included recording all the hardware-related complications observed up to January 2016. Usually, such complications need medical treatment shortly after onset. Data was collected through patients' medical records. Patient follow-up also included an in-person neurological examination. For patients unavailable for the examination, medical records were obtained by follow-up telephone interviews. During the follow-up period, if a patient died, the cause of death and recent medical history of the patient were collected through telephone or other contact methods. If death occurred during a hospital stay, the above data was collected from the hospital records.

Data analysis

In addition to the basic demographic information of the patients, a descriptive analysis of the collected hardware-related complications and causes of death was conducted to identify any common factors or causes of death, and thus to identify the corresponding measures needed to rectify the problem (if possible).

Results

The cohort included a total of 515 patients with PD. Of those, 37 cases were excluded from the study due to loss of contact (ie, no follow-up), so the analyzed patient cohort consisted of 478 cases. Of the patients with PD who underwent DBS treatment, 325 (63%) were male, and 190 (37%) were female. The average age at the time of surgery was 57.5 ± 11.0 years. As shown in Table 1, there were 41 cases of death among the 478 patients. Two of the 41 deaths occurred during the first week after surgery due to intracranial hemorrhage. Among the remaining 39 cases (8.2%), the causes of death were pneumonia ($n=13$), asphyxia ($n=8$), organ failure ($n=6$),

Table 1 Information on cases of patient deaths (n=41 total)

	Male	Female
Frequency (cases)	21	18
Age (years)	61.9±1.4	61.7±3.2
Disease duration (years)	9.4±0.6	10.6±0.9
Years of postoperative survival	7.4±0.8	6.0±0.7
Cause of death	Pneumonia (6), asphyxia (4), organ failure (4), cancer (2), suicide (2), chest bleeding caused by fall (1), cerebral hemorrhage (1), and ketoacidosis (1)	Pneumonia (7), asphyxia (4), suicide (2), organ failure (2), cancer (1), myocardial infarction (1), and cerebral infarction (1)
Target	STN**	STN***

Notes: Data presented as mean ± standard error. There was no statistically significant difference in sex, age, duration of disease, and postoperative survival ($P>0.05$). **One case underwent explantation of the STN leads, and new implantation into the GPI. ***The target was the bilateral GPI in two cases.

Abbreviations: STN, subthalamic nucleus; GPI, globus pallidus internus.

and cancer (n=3). One of the patients had other problems previously: the patient had suffered a fall, and had a history of lacunar infarction, myocardial infarction, type 2 diabetes, and cerebral hemorrhage. There were also four cases of suicide. Thus, the cause of death with the highest frequency in the patient group was pneumonia (38.5%).

Based on the follow-up records, 22 (4.6%) patients reported hardware-related complications (Table 2). These included immune rejection reactions (n=11), infection (n=9), and hardware failure (n=2). One patient had an immune rejection reaction followed by an infection. The immune rejection reactions seen in patients mainly manifested as skin irritation or ulceration stimulated by the DBS electrode, and/or an exposed extension wire and IPG. Hardware failure included one case of electrode fracture and one case of IPG failure.

The application of DBS has gradually broadened as a neurosurgical indication outside of PD because of its advantage in terms of minimal invasiveness, high safety, and reversibility.⁷ Although generally well tolerated, as with any surgery, it has potential complications. Among them, hardware-related complications are the most common non-hemodynamic complications; reports indicate that 5%–9% of cases may have such complications.^{8,9} In general, device failure (lead or extension wire fracture) and immune rejection are the two most common complications.

DBS hardware, being an artificial implant, is prone to infection. In recent years, it has been reported that the average perioperative risk of infection per person is 4%–6%.^{10–12} To prevent infection, routine perioperative use of antibiotics is recommended. In the study center, ceftriaxone (or levofloxacin for allergic patients) was usually given for 3 days after surgery, prophylactically. This is due to the fact that once infected, the treatment efficacy of antibiotics alone for non-superficial infections involving hardware is often limited. In such cases, treatment requires surgical debridement or even removal of all the hardware. Normally, in the

study center, attempts are made to keep at least the DBS electrode, to prevent the need for replacement neurosurgery. Such surgery is usually more time-consuming than the initial operation, and more invasive than the replacement of the other hardware. Reports in literature also support the combination of surgical debridement and antibiotic therapy for salvaging the hardware.^{13,14} For cases that need complete removal of the DBS system, stereotaxic unilateral pallidotomy is a surrogate treatment that can improve the quality of life of patients.

It was found that infection due to immune rejection is not an uncommon hardware-related complication. Such a complication is indicative of a poor outcome from DBS treatment in the future. To reduce the possibility of hardware removal due to rejection, a one-time intramuscular injection of betamethasone is done after surgery at the study center. Corticosteroids are also used to treat DBS lead edema; however, neither infections nor psychiatric adverse effects have been observed with this treatment.¹⁵ Regional subcutaneous fluid accumulation is a common clinical manifestation of rejection reactions. Short-term treatment using methylprednisolone after fluid removal through puncture is commonly conducted to provide the best chance of avoiding surgical debridement or hardware removal. While improving the antigenicity of DBS devices is one way to reduce rejection, with the current medical technology, the occurrence of immune rejection is frequently avoidable. Research on biomedical materials suggests that covering the DBS equipment with an insulating layer of biofilm-like material could reduce the risk of rejection.

It is reported that the incidence of wire fracture or disconnection is 2%–3%.⁹ Electrode shift is not usually a complication in the short term. However, a sudden, large patient head movement due to trauma or other causes can lead to deviation of the electrode contact point from the target. In such cases, surgery is necessary to adjust the electrode

Table 2 Information about hardware-related complications

Case no	Sex	Age at surgery (years)	Year of surgery	Onset of complication (years postsurgery)	Target	Complications	Treatment
1	F	67	2000	1	Bilateral STN	Right electrode fracture	Electrode reimplantation
2	M	47	2003	4	Bilateral STN	IPG erosion	Move IPG to other side
2	M	47	2003	7	Bilateral STN	Electrode and wire exposure	Removal of DBS system
3	M	60	2003	6	Bilateral STN	Skin abrasions were due to IPG rejection	Move IPG to other side
4	M	66	2003	6	Bilateral STN	Exposed electrode	Big skin flap embedding
4	M	66	2003	8	Bilateral STN	Exposed electrode and extension wire	Electrode removal
5	M	51	2003	6	Bilateral STN	Exposed electrode	Reimplantation but removal half year later
6	F	45	2003	1	Bilateral STN	Exposed electrode	Big skin flap embedding
6	F	45	2003	2	Bilateral STN	Exposed electrode and IPG	Removal of DBS system
7	M	56	2003	9	Bilateral STN	Exposed electrode	Reimplantation half year after electrode removal
8	M	60	2004	5	Right STN	Exposed electrode, extension wire, and IPG	Scalp debridement
9	M	42	2004	4	Bilateral STN	Exposed IPG	Change IPG from Kinetra to Soletra
9	M	42	2004	6	Bilateral STN	Exposed extension wire	Big skin flap embedding over connector
10	F	48	2005	4	Bilateral STN	Exposed extension wire	Move extension wire from right to left
10	F	48	2005	7	Bilateral STN	Exposed extension wire and left electrode	Removal of left DBS system and left pallidotomy
11	M	43	2005	6	Bilateral STN	Erosion of IPG and infection	IPG position adjustment
12	F	57	2006	4	Bilateral STN	Exposed left electrode	Big skin flap embedding
12	F	57	2006	6	Bilateral STN	Exposed left electrode and extension wire	Removal of left DBS system and left pallidotomy
13	M	53	2006	3	Bilateral STN	IPG erosion	IPG position adjustment
14	F	58	2006	6	Bilateral STN	IPG failure	Change IPG
15	F	61	2007	2	Bilateral STN	IPG and wire infection	Removal of DBS system
16	M	47	2008	1	Bilateral GPI	Exposed extension wire	Move extension wire from right to left
16	M	47	2008	3	Bilateral GPI	Exposed extension wire and electrode	Removal of DBS system
17	F	52	2008	1	Bilateral STN	Rejection to IPG and electrode	Removal of DBS system
18	M	47	2009	1	Bilateral STN	Electrode infection	Removal of DBS system
19	M	61	2010	1	Bilateral STN	IPG and wire infection	Removal of DBS system
20	F	64	2010	2	Bilateral STN	Unilateral electrode infection	Removal of DBS electrode and perform unilateral pallidotomy
21	M	67	2010	1	Bilateral STN	IPG and wire infection	Removal of DBS system
22	M	66	2011	2	Bilateral STN	Exposed electrode	Big skin flap embedding and retained electrode

Abbreviations: F, female; M, male; STN, subthalamic nucleus; IPG, implantable pulse generator; DBS, deep brain stimulation; GPI, globus pallidus internus.

and/or restore the connections of the DBS system. Overall, the following precautionary measures will be taken for high-risk patients: fixing the extension wire to the parietal bone with a titanium nail and cap; using a bigger and curled incision; and in patients with allergic history, especially those with diabetes as well, unilateral pallidotomy and unilateral DBS are recommended. Once immune rejection

has occurred, scalp debridement and bigger-curl skin flap embedding will be performed initially, after which the extension wire and/or IPG may be moved to the other side. Finally, removal of the DBS system and unilateral pallidotomy are the last resort.

This retrospective study showed that the 3-year survival rate of patients with PD who underwent DBS treatment at

the study center was 98.6%, and the 5-year survival rate was 96.4%. These rates are higher than those reported in previous studies, which are approximately 97% at 3 years, and 89%–90% at 5 years.^{16,17} The mean age of death was reported to be <63 years.¹⁶ In addition, the average age of the patients at the time of surgery was slightly higher (57.5 years).¹⁶ However, it was not possible to exclude the effect of increased life expectancy. It was noted that two patients in the cohort died within 1 month after the surgery, which is <1% of the total patient population. There were no deaths directly due to hardware-related complications, which is consistent with the known DBS safety data.^{18,19} It should be noted that the survival rate of patients with PD after DBS treatment is probably higher than previously estimated.

Among the various causes of death, pneumonia and malignancy are the most noted. Results from other published studies also indicate that pneumonia is a common cause of death in PD.^{20,21} Besides pneumonia and malignancy, asphyxia and multiple-organ failure were also the main causes of death observed in the study center. However, other studies cite stroke and heart disease as common causes of death.^{21,22} Dysphagia, or disordered swallowing, is an inevitable consequence of the disease progression in PD. Indeed, aspiration pneumonia secondary to dysphagia is a main cause of death in PD. Including the results reported herein, no published work has identified clinically significant robust functional improvement or decline in swallowing function with STN DBS.²³ Identifying the most common potentially lethal complications could allow for earlier detection and treatment in the clinic, extending the life expectancies of patients further.

One critical issue is swallowing-related motor impairment in PD. Among the 39 deaths in this study group, the 15 cases of pneumonia, seven cases of asphyxia, and three cases of multiple-organ failure were all associated with swallowing impairments. These swallowing-related disorders are likely the result of stereotyped movement and motor impairment of the epiglottis and throat muscles.^{23,24} Kanna and Bhanu also reported a high prevalence of swallowing-related diseases in patients with PD, the severity of which was associated with the duration and severity of PD.²⁵ Therefore, it is particularly important to pay attention to the signs and symptoms of swallowing-related disease, for both early intervention and improvement of quality of life. There have been considerable debates over whether swallowing-related diseases in PD can benefit from DBS. A majority of patients showed improved motor function and observable improved eating function with weight gain; however,

some patients suffered from hoarse voice and experienced suffocation after surgery.²⁶ As a result, DBS therapy has not been recommended as a routine treatment for the relief of symptoms of swallowing-related illnesses.²⁷ Instead, active early-stage rehabilitation and increased awareness of voluntary cough are recommended.²⁵

Limitations

This study has certain limitations. First, of 515 patients, 37 (7.2%) had to be excluded for lack of follow-up. Although this should not cause a serious bias, it may have a modest impact on the effectiveness of research on intervention. Moreover, this was a single-center retrospective analysis. Neither the practical deviation of the research team nor other chronic diseases such as hypertension and diabetes have been described as confounding factors. Each of these conditions is likely to alter hardware-related complications and the causes of death.

Conclusion

DBS has become one of the most common surgical treatments for patients with PD, especially those with strong tremor or motor fluctuations. DBS treatment in patients with PD is expected to increase survival time. It was found that the death of these patients is usually not related to the disease itself or complications associated with the surgery. Pneumonia, malignant tumors, asphyxia, and multiple-organ failure are the important causes of death. Swallowing-related problems may be the most important clinical symptom in late-stage PD, since the symptom cannot be stabilized or improved by DBS alone, and is potentially lethal. In the future, study using a prospective analysis of the impact of DBS on the survival of patients with PD is needed, as is comparative data between DBS and the currently effective drug treatments, in order to determine the most effective treatment plan for different stages of PD. Regarding hardware complications, prophylactic antibiotics and steroids or anti-histamine drugs may reduce the risk of infection. It is imperative to identify high-risk patients for whom a therapeutic approach that does not involve an implantable device is more suitable, for example, pallidotomy and possibly transcranial ultrasound.

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