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Comments

This is an interesting case report that highlights the importance of the angle of approach in deep brain stimulation (DBS) surgeries. The trajectory and the angle of implantation dictates the final location of the DBS within the various structures and influences the benefits and side effects. The authors show in this one case that a more anterior and shallow angle of approach encompassing the VOP/VIM target has better efficacy than a posterior and vertical approach to the VIM. Additional studies are needed to further investigate this concept.

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This is an interesting paper reporting that changing the angle of trajectory may influence the efficacy of deep brain stimulation. Certainly it reflects my experience with essential tremor in that pure VIM stimulation may not suppress ET effectively. I target the VOP and VIM as much as I can in the approach. Essential tremor is not benign at all, the tremor can become resistant to stimulation in a significant number of patients. I therefore advise my patients with ET to turn the stimulator on only if they need to do a task.

The authors of this paper suggest an extremely shallow angle that straddles VOP and VIM with good effect. I wonder if this might in some cases cause an unsightly forehead scar. Nevertheless this is an interesting case report.

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Review

Identification and management of deep brain stimulation intra- and postoperative urgencies and emergencies☆

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ABSTRACT

Deep brain stimulation (DBS) has been increasingly utilized for the therapeutic treatment of movement disorders, and with the advent of this therapy more postoperative urgencies and emergencies have emerged. In this paper, we will review, identify, and suggest management strategies for both intra- and postoperative urgencies and emergencies. We have separated the scenarios into 1 – surgery/procedure related, 2 – hardware related, 3 – stimulation-induced difficulties, and 4 – others. We have included ten illustrative (and actual) case vignettes to augment the discussion of each issue.

Contents

☆ The review of this paper was entirely handled by the Co-Editor-in-Chief, Zbigniew Wszolek.

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1. Introduction

Neurosurgical procedures for basal ganglia disorders may result in urgent or emergent management issues. Postoperative urgencies and/or emergencies should be identified and treated in an expeditious manner. Deep brain stimulation (DBS) has been increasingly utilized for addressing neurologic and neuropsychiatric disorders [1,2], and with the increasing number of DBS cases being performed each year, there has been a commensurate increase in the number of issues relating to the surgical, the procedural, and to the stimulation-related phenomena. Some of these issues have manifested themselves as movement disorders (e.g. dyskinesia, ballism, dystonia), although the majority have presented in other ways [3–5]. In this paper, we have separated the potential scenarios into 1 – surgery/procedure related, 2 – hardware related, and 3 – stimulation-induced phenomena. The discussion has been augmented by the use of clinical vignettes which illustrate the diagnosis and management of both urgent and emergent situations. Complications of DBS have unique manifestations, and diagnostic criteria and management have not been fully established in some cases. Therefore, it is possible that clinicians may overlook DBS-induced complications, and delay the appropriate management. This delay may unnecessarily result in secondary complications. The aim of this paper is to review urgent and emergent DBS-associated situations to provide recommendations for appropriate management.

2. Methods

Complications with DBS-specific manifestations have been specifically selected for this review, and a PubMed based literature search was performed for each issue. We queried the Institutional Review Board (IRB) approved DBS database of University of Florida Movement Disorders Center (UFMDC) for the illustrative cases from the period between July 2002 and June 2009.

2.1. Surgery/procedure related urgencies/emergencies

2.1.1. Intracranial hemorrhage

Case 1. A 73-year-old man with a 16-year-history of Parkinson's disease (PD) underwent unilateral subthalamic nucleus (STN) lead implantation. There was no history of hypertension, diabetes mellitus (DM), or coronary artery disease (CAD). Following the procedure, he became somnolent, and a postoperative computed tomography (CT) scan revealed a hematoma in the left lateral ventricle (Fig. 1B). There was involvement of the third ventricle and the Sylvian aqueduct. The patient developed acute obstructive hydrocephalus that necessitated emergent ventriculostomy. He convalesced for one week postoperatively, and then developed a deep venous thrombosis, an aspiration pneumonia, atrial fibrillation, a urinary tract infection, and sepsis. The total hospitalization was extended to 40 postoperative days. Following eight months of rehabilitation and anticoagurant therapy he has recovered, and implantation of Implantable Pulse Generator (IPG) was scheduled.

Hemorrhage is an emergent adverse event that may be seen following DBS, and may result in significant morbidity or rarely even death. Hemorrhages following DBS may include intracerebral (ICH), intraventricular (IVH), subdural (SDH), subarachnoid (SAH) and epidural (EDH) (Fig. 1). Hemorrhagic complications have been assumed to be due to damage to the blood vessels by the microelectrode recordings (MERs) and/or macrostimulation passes, and it has been discussed that multiple MERs and/or macrostimulation passes may increase the incidence of hemorrhagic complications (debated but generally accepted among the experts) [6–8]. Intracranial hemorrhage can be diagnosed by CT scan which may be sought in the postoperative period and is usually performed as a result of a mental status change and/or a focal neurological deficit. The incidence of hemorrhage varies from 0.6 to 3.3% [7,9–13]. Intracranial hemorrhage can precipitate secondary complications such as pneumonia, pulmonary embolus, and urinary tract infection. A recent German multicenter study revealed an overall 30-day postoperative mortality rate of 0.4% (5 of 1183 patients), and mortality due to hemorrhage in 2 of 5 patients [14]. Delay of identification and management of ICH can result in significant morbidity, therefore emergent care should be employed to prevent both primary and secondary complications. When ICH is encountered it mandates immediate neurosurgical consultation, preferably by the neurosurgeon who implanted the DBS system, although this is not always possible. Most patients can be managed conservatively, however if operative intervention for evacuation is deemed necessary every attempt should be made not to remove the DBS hardware (Table 1). Patients requiring evacuation as well as those not requiring surgery have the potential for good recovery.

2.1.2. Venous infarction

Case 2. A 60-year-old man with PD underwent a staged unilateral globus pallidus interna (GPi) DBS. He was discharged on postoperative day #1 following an uncomplicated hospital course, but later that day he began to develop left-sided weakness, lethargy, and confusion which peaked on postoperative day #2. He presented to the emergency room (ER) on postoperative day #4. A head CT scan revealed hemorrhage spreading from the center of the DBS lead. The region was surrounded by edema (Fig. 1D). The diagnosis of venous infarction was made and he was conservatively managed. Following several months, his neurological status returned to baseline, and his DBS was effectively programmed to address both motor fluctuations and parkinsonism.

Venous infarction has been associated with damage to a cortical vein that may occur during DBS surgery. Cerebral edema and hemorrhage may slowly develop and are usually the result of venous stasis or venous hypertension. These phenomena are thought to occur as a result of venous obstruction which usually traces to the damaged cortical vein. Venous infarction can be characterized by a delayed clinical onset with edema and possibly hemorrhage along the path of the DBS lead [15]. These features may be absent in some cases. Importantly, the head CT may not reveal an obvious lesion in the immediate postoperative period, and a repeat CT may be necessary to confirm diagnosis. The prognosis is usually positive in venous infarction occurring post-DBS [7,16]. Careful preoperative targeting using a high quality contrasted MRI will aid in avoiding cortical veins, and may prevent this complication [7]. If the diagnosis of venous infarction is made postoperatively, the management should include optimizing the venous return (e.g. elevate the head of the bed), managing blood pressure, avoiding dehydration, and initiating early rehabilitation (Table 1).

2.1.3. Dyskinetic storm

Postoperative dyskinesia is a relatively common phenomenon associated with STN DBS, especially in PD patients who preoperatively suffered from severe medication-induced dyskinesia [4]. Microelectrode recording, cannula placement and/or lead placement may all induce dyskinesias especially in patients with PD. Acute and severe exacerbation of dyskinesias (dyskinetic storm) in the operative setting has been previously reported and may be a feature associated with a positive prognosis [3]. In severe cases, dyskinesia may be associated with dyspnea and rhabdomyolysis [17,18], and emergent administration of sedative agents (such as IV propofol) may be required [3] (Table 1). Dyskinesia may also be induced by DBS placement in a delayed fashion [19], and dyskinetic storm may be encountered in the clinical setting following DBS programming. Management of dyskinesia in the clinical settings will also be discussed in the "*Stimulation-related motor symptoms*" section of this review.

2.1.4. Postoperative behavioral and cognitive problems

Postoperative cognitive and behavioral decline is a common DBS-related adverse event. It is usually temporary, but in patients with preoperative cognitive dysfunction it may persist. The incidence of confusion has been recently reported as 5% in a large single center study [20], but rates may vary depending on preoperative comorbidities, target site, and whether staging of operative sides is employed (i.e., as opposed to same-day simultaneous bilateral DBS implantation) [4,21–23]. The incidence of behavioral and cognitive problems may be higher in STN DBS when compared to other targets [4,23–25]. A recent randomized double-blind study revealed a higher incidence of cognitive adverse events in patients with STN DBS when compared to GPi DBS [23]. Also verbal fluency seemed worse in STN and the change was reported as more surgery-related rather than a stimulation-related effect (i.e. it occurred in the off STN condition as well as the on STN DBS condition during blinded testing) [23].

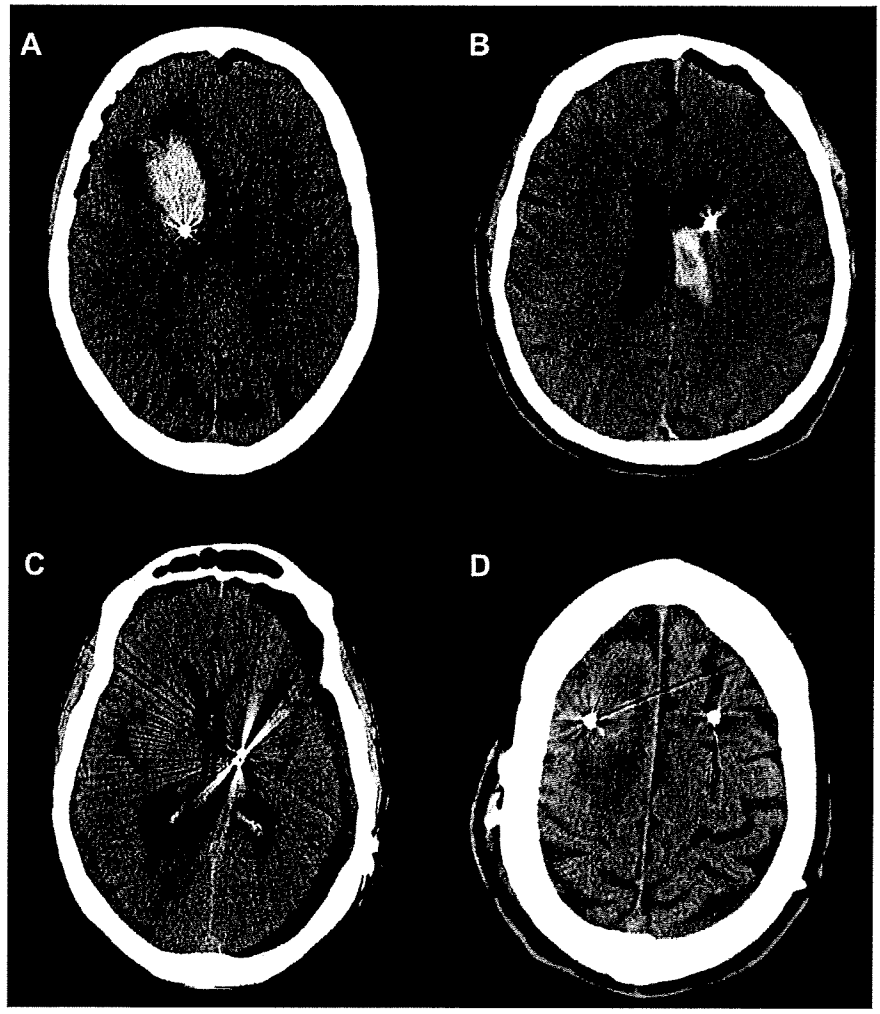

Fig. 1. Computed tomography (CT) scan images of the many types of hemorrhage that may be encountered following DBS lead implantation. This panel of CT images reveals examples of intracerebral hemorrhage (A), intraventricular hemorrhage (B), subdural hemorrhage (C), and venous infarction (D).

Anticholinergics (including not only anti-Parkinsonian medications but also medications for neurogenic bladder) may also increase the risk of postoperative cognitive problems, and may need to be discontinued [26]. It is important for clinicians to keep in mind that advanced age and/or pre-existing neurological compromise may predispose patients to mental status changes following DBS, and this is a compelling reason for centers to perform preoperative neuropsychological screening [21].

The management of postoperative behavioral and cognitive problems should include a diagnostic workup of potential underlying causes that may exacerbate and/or contribute to the clinical condition. These may include urinary tract infections, hemorrhage or medications related phenomena. If no underlying treatable cause can be identified, the clinician should utilize pharmacotherapy and a multi/interdisciplinary approach to manage the behavioral change(s). This approach may be facilitated in select cases by an inpatient admission.

Patients may become restless and violent postoperatively due to hallucinations/delusions, and this situation may require urgent/emergent care. In these cases, conventional neuroleptics are usually contraindicated, however using selective dopaminergic blockers such as quetiapine or clozapine may be useful [27] (Table 1). Non-selective dopaminergic blockers (e.g. olanzapine, risperidone, haloperidol, etc.) that have been commonly employed for the treatment of behavioral emergencies have also been observed to lead to drug-induced parkinsonism as well as other movement disorders [28,29].

2.1.5. Suicide attempt or ideation

Case 3. A 54-year-old woman with PD and depression who had a left DBS implantation two years prior to presentation was brought to the emergency room following a suicide attempt by drug overdose. Passive suicidal ideation was noted on her psychiatric evaluation prior to DBS.

Several reports have revealed cases of attempted and completed suicide occurring following DBS [30–32]. DBS may increase the risk of suicide when compared to the general population, but not necessarily when compared to a PD population (without DBS) [31,33]. A recent multicenter study revealed that preoperative history of impulse control disorders or compulsive medication use, postoperative depression, postoperative apathy, and being single were strongly associated with suicide attempts [33]. Previous suicide attempts, younger age of the patient, and younger onset of PD were also revealed to be associated with suicide attempt within the same study cohort. Therefore, screening for suicidal ideation following DBS should be routine, and if discovered, it should be treated as an emergency. Clinicians should admit patients to the hospital for multi/interdisciplinary care, which may include cognitive behavioral therapy, counseling, and/or medication/stimulation adjustment(s) (Table 1). Whether DBS results in disinhibition or impulsiveness and ultimately contributes to suicidal ideation or suicide remains controversial [34]. Vigilant pre and postoperative screening for depression and suicidal ideation are recommended. Preoperative neuropsychological and psychiatric evaluation is highly recommended as a preventative measure [21,32]. Advanced PD patients are likely to have cognitive and/or mood disturbances, and neuropsychologists can play an important role for screening out these issues. Recently, there have been several reports of suicide in dystonia DBS highlighting that this issue may not be solely related to PD [30,31,35].

2.1.6. Myocardial infarction

Case 4. A 58-year-old male with PD, coronary artery disease (CAD) (previously treated with angioplasty), hypertension, diabetes mellitus (DM), and hyperlipidemia underwent unilateral STN DBS placement. An implantable pulse generator (IPG) was placed four weeks following the DBS lead. Following IPG implantation

Table 1
Postoperative surgery and hardware related urgencies and emergencies.

Issue	Routine/urgent/emergent	Management
Intracerebral hemorrhage	Emergent	If the hemorrhage is very large, an emergent craniotomy may need to be performed.
Intraventricular hemorrhage	Emergent	Ventriculostomy if necessary may be performed for obstructive hydrocephalus.
Subdural hematoma	Emergent	If acute and symptomatic, an emergent craniotomy may be performed in select cases. If chronic, a burr hole irrigation may be performed, or it may be watched conservatively.
Epidural hematoma	Emergent	An emergent craniotomy should be performed immediately in severe cases.
Venous infarction	Urgent/emergent	Conservative therapy. An emergent craniotomy may be performed if hemorrhage is life threatening.
Dyskinetic storm	Urgent	Sedative agents may be administered in select cases. Reducing the dopaminergic medication may help. In some cases ICU care is necessary.
Behavioral/cognitive issues	Urgent/emergent	Identify and treat the underlying issues. Selective dopamine blockers (e.g. quetiapine, clozapine) may be used, but non-selective blockers should be avoided if possible.
Suicide ideation/attempt	Emergent	Evaluation for an underlying issue such as battery life and/or unintended on/off. Admit the patient to the hospital for multidisciplinary care including behavioral therapy, counseling, medication adjustment and/or stimulation adjustment.
Air embolus	Emergent	Wax edges of the burr hole, lower patient's head, jugular venous compression, administer oxygen
Infection-UTI	Routine/urgent	Hydration and appropriate antibiotics, case should be taken to adjust PD medications if necessary as levels may be altered by antibiotics.
Infection-lead	Emergent	The lead should be removed and appropriate antibiotics should be administered.
Infection-IPG	Urgent	The IPG and usually the extension cable should be removed and appropriate antibiotics should be administered.
Lead fracture	Urgent	Lead replacement, if an appropriate candidate.
Lead electrical short	Urgent	Lead replacement, or potentially reprogramming at a different contact
Lead migration	Urgent	Lead replacement, surgical alteration of lead position, or potentially reprogramming at a different contact.
Lead misplacement	Urgent	Lead replacement.
IPG malfunction	Urgent	IPG replacement, manage potential rebound symptoms.

the patient died in his sleep on postoperative day one from a myocardial infarction.

Assessment of medical comorbidities must be performed on all patients undergoing DBS surgery [21]. Clinicians should be aware that patients taking medications that can affect the cardiovascular system such as bromocriptine, and tricyclic antidepressants (TCAs) may be at increased risk when undergoing general anesthesia [36]. The incidence of angina and arrhythmia following DBS surgery has been reported as 0.3% in a recent large single center study [20]. A history of CAD may increase the perioperative risk of MI and angina. High risk patients should be carefully monitored (pre and postoperatively), and they may even require extra monitoring following general anesthesia. Cardiac or pulmonary symptoms in the postoperative period should be treated as an urgent, and possibly even emergent complications. Although this complication can be encountered following any surgical procedure, chest pain in the region surrounding the IPG DBS skin incision may be erroneously attributed to a DBS-related issue rather than to a cardiac related issue [37]. Clinicians should be aware that the risk of comorbidities and medications, and that postoperative chest pain following DBS/IPG implantation can present or evolve into urgent or emergent issues.

2.1.7. Air embolus

Air embolus a relatively uncommon complication of neurosurgical procedures. However, clinicians should be aware that the incidence of air embolus during DBS surgeries has been reported to be as high as 3% in a recent report, and DBS-related air embolus may manifest differently from other neurosurgical procedures, since during DBS the procedure is performed awake rather than under general anesthesia [38,39]. When the neurosurgeon is preparing the burr hole for microelectrode recording and/or macrostimulation, air embolus may occur with tachycardia, a rise in the end tidal CO_2, and cough. This reaction is typical of entrainment of air into the venous system. It is important to preoperatively position the patient's head as close to supine as possible to minimize this complication. In a recent series, Hooper et al. reported the potential use of an external Doppler device to enhance monitoring for air embolus during DBS [39]. These authors also noted that the cough was the best clinical indicator to pick up an air embolus. When encountered, the head position should be adjusted (lower the patient's head), bone edges of the burr hole should be waxed, the surgical field rigorously irrigated, and the patient vigorously supported from a cardiopulmonary standpoint. Additionally, having the neurologist, nurse or physiologist temporarily compress the neck (to inhibit venous return) may aid the neurosurgeon in identifying the problematic region, and in quickly correcting the situation (Table 1).

2.2. Hardware-related urgencies/emergencies

2.2.1. Hardware infection

Case 5. A 43-year-old man with a nine-year-history of PD underwent unilateral STN DBS. He arrived for a routine clinic appointment and staple removal on postoperative day seventeen. Following the staple removal there was purulent drainage from the cranial incision site, and the pectoral incision revealed tender erythema (Fig. 2). He was admitted to the hospital urgently, and the IPG and the extension wire were both removed. A course of intravenous antibiotics was completed prior to re-implantation.

Case 6. A 71-year-old man with a history of medically refractory essential tremor (ET) underwent a unilateral thalamic DBS implantation. Four weeks following surgery, the patient reported to the clinic for routine follow up care. Headache and progressive dysphagia were the chief complaints, and a head CT scan revealed a brain abscess along the DBS lead tract. The CT scan demonstrated an edematous lesion surrounding the DBS lead which was enhanced with contrast media (Fig. 3). He was admitted for emergent craniotomy, DBS lead removal and abscess drainage.

Hardware related infections are not uncommon in DBS. The incidence of infection and/or erosion following device implantations has been reported to range between 0 and 15.2% [10,40–46]. Even the most vigilant surgical technique cannot guarantee the absence of postoperative infectious complications. The devices in these scenarios may require emergent removal, in contrast to the management of ICH, which may not require lead removal (Table 1). Cultures should be sent anytime hardware is removed or a potentially infectious pocket aspirated. Although several factors may be related to infection rate, pre and postoperative prophylactic antibiotics may prevent hardware infection, however the evidence base for their use is

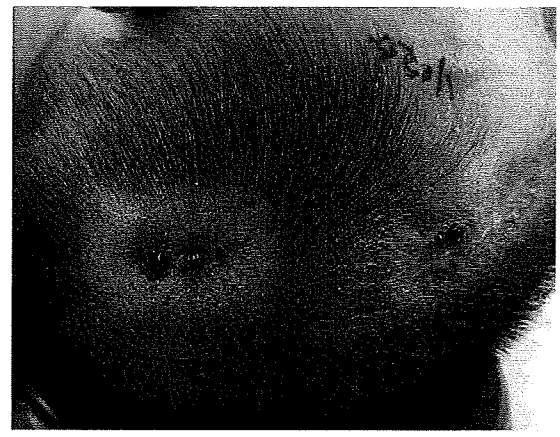

Fig. 2. Infection in the cranial skin incision. The illustration reveals purulent drainage from the cranial incision.

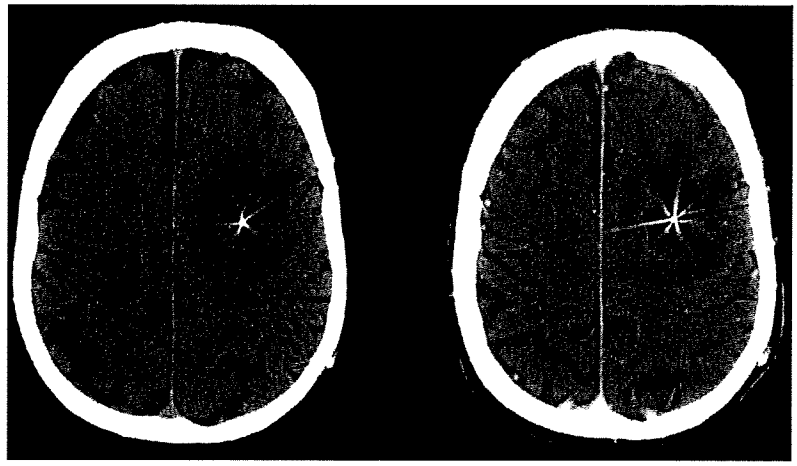

Fig. 3. Computed tomography (CT) scan images of a brain abscess following DBS lead implantation. A CT scan image without contrast (left) revealed a low density area which indicated an edematous lesion surrounding the DBS lead. The lesion was enhanced with contrast media (right).

weak [44,46]. One recent study did however report a reduction in the infection rate by locally injecting anti-staphylococcal antibiotics (e.g. neomycin, polymixin) directly into the operative wound [46].

There are several factors that may impact the management of a DBS infection. These include 1 – whether the infection is deep or superficial, 2 – whether the brain lead is involved, and 3 – whether there are single or multiple sites of involvement [40]. A superficial infection may be managed in select cases in a non-operative and conservative fashion, however a deep infection may require emergent hardware removal. When the brain lead and/or multiple sites are involved, many DBS teams elect to remove all hardware (lead, extension, and IPG). In cases where only the IPG or extension cable appears infected, there is an option to remove only the purported infected hardware and to attempt to preserve the brain lead. Following a course of 6–8 weeks of IV antibiotic therapy, device(s) re-implantation may be possible.

2.2.2. *Hardware malfunction*

Case 7. A 76-year-old woman with a history of essential tremor (ET) who underwent a left thalamic DBS implantation three years prior presented to clinic with sudden tremor recurrence. A few days before her presentation, following a mammogram she experienced a tingling sensation in the right upper extremity with an abrupt loss of benefit in her right upper extremity tremor. When the device was checked the impedance was discovered to be greater than 2000 Ω, and a chest x-ray revealed a flipped IPG and a twisted extension cable (Fig. 4). A fracture of the extension cable was suspected, and replacement of the cable resolved the issue.

When a DBS patient reports sudden loss of efficacy, the clinician should consider hardware malfunction [4,47]. Mechanical stress to the device may result in lead fracture, a break in the extension cable, or an IPG failure. Blomstedt et al. reported 7 of 8 broken electrodes in their cases were encountered in patients with ET, and they speculated head tremor may have contributed to the adverse event(s) [44]. Compulsive manipulation of the IPG device, referred to as "Twiddler's syndrome", has also been reported to result in extension cable fractures [48].

The DBS programming/interrogation device should be used to measure the impedance and current drain for each of the four lead contacts. This procedure will assist in verifying the physical integrity of the DBS system. A high impedance along with a low current drain may be consistent with a lead fracture or with an extension cable break. Alternatively a low impedance with possible high current drain may be supporting evidence for a short circuit. In short circuits the patient will frequently complain of a shock-like sensation when palpating the IPG or when pressing along the extension cable tract. A plain film x-ray should be obtained to search for a fracture along the course of the lead or extension wire (Fig. 5). When the location of the problem cannot be precisely identified, the next step is to replace the extension wire and to retest impedances in the operating room setting. This procedure may save replacement of the intracranial lead in select cases [47]. Clinicians should always keep in mind that contacts with normal impedances/current

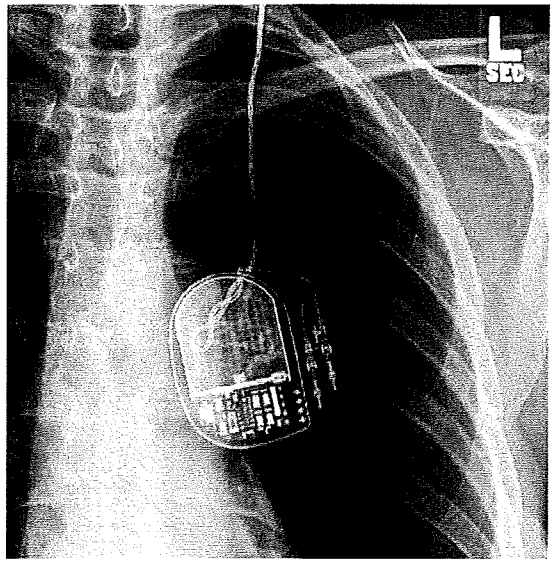

Fig. 4. A chest x-ray revealed a twisted extension cable and flipped IPG following a mammography. These features have been referred to as the twiddler syndrome.

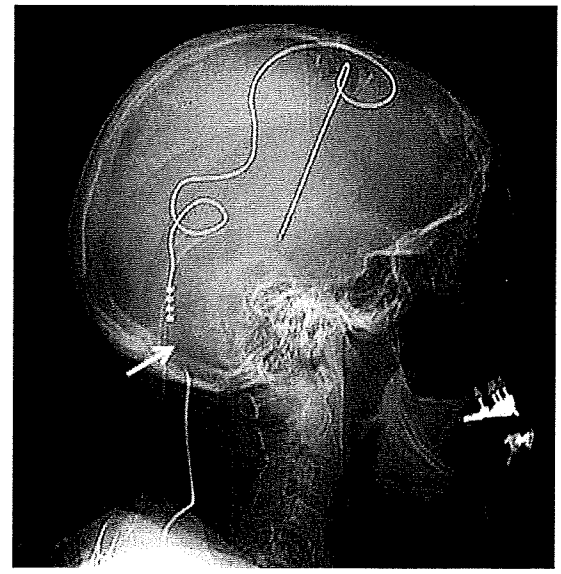

Fig. 5. A skull x-ray revealed an extension cable fracture.

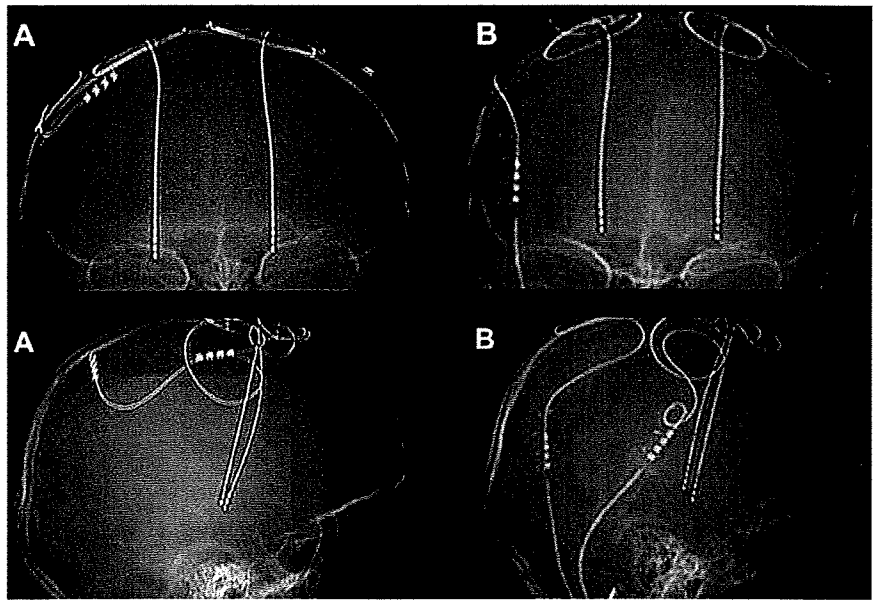

Fig. 6. Dorsal lead migration shown by serial x-rays. A) A skull x-ray at one month post-implantation. B) A skull x-ray at eight months pre-repeat implantation. Left and right leads had deviated from baseline.

drain values, are potentially programmable. An attempt to reprogram these functioning contacts should be sought prior to recommending replacement (Table 1).

2.2.3. Lead migration

Case 8. A 7-year-old boy with DYT-1 positive generalized dystonia underwent bilateral GPi DBS. After an initial dramatic response, his benefit deteriorated over the first year. Measurement and comparison of his DBS leads revealed dorsal lead migration (Fig. 6). His head circumference was measured and found to be 51.5 cm preoperatively and 53 cm 30 months later. Repositioning the DBS leads recaptured benefits.

Case 9. A 26-year-old man developed tardive dystonia following exposure to a neuroleptic drug used to address his severe depression. He subsequently underwent bilateral GPi DBS. Preoperatively he suffered severe and painful retrocollic head jerks. Postoperatively his subjective pain and head jerking clinically improved (pain approximately 50+% and movement disorders approximately 40–50%). Six months following the operation the benefits waned, and a CT scan revealed that the left and the right leads had migrated 15.6 mm and 4.6 mm ventrally from their initial position (Fig. 7). The patient underwent successful lead replacements.

Lead migration, either dorsal or ventral, can result from a malfunction of anchoring devices, skull growth, or vigorous head movements [47,49]. Yianni et al. reported that 3 of 133 patients (2.3%) experienced lead migration [49]. All three patients had dystonia, and the authors hypothesized that axial movements contributed to lead migration. When ventral lead migration is noted in a patient with GPi DBS, clinicians should be cautious as the ventral lead migration may result in severe mood changes due to the spread of the stimulation to other regions such as but not limited to the amygdala [50]. Skull growth in children is another cause of lead migration as illustrated by case 7. When lead migration is noted, changing the active contact (deeper or shallower depending on the direction of migration) should be attempted in most cases prior to surgical revision [51] (Table 1). This adverse event highlights the importance of examining postoperative imaging.

2.2.4. Lead misplacement

Case 10. A 60-year-old man with a history of PD underwent bilateral STN DBS at an outside institution 5 years prior to presentation to our clinic. He reported a lack of benefit from DBS, and repeated programming in the past had not improved his situation. An MRI scan revealed lead misplacement (Fig. 8). The patient was unwilling to undergo a lead replacement because of a combination of claustrophobia and fear of the surgical suite.

Lead misplacement is a not uncommon complication of DBS surgery and has been reported to be associated with technical error, intraoperative brain shift

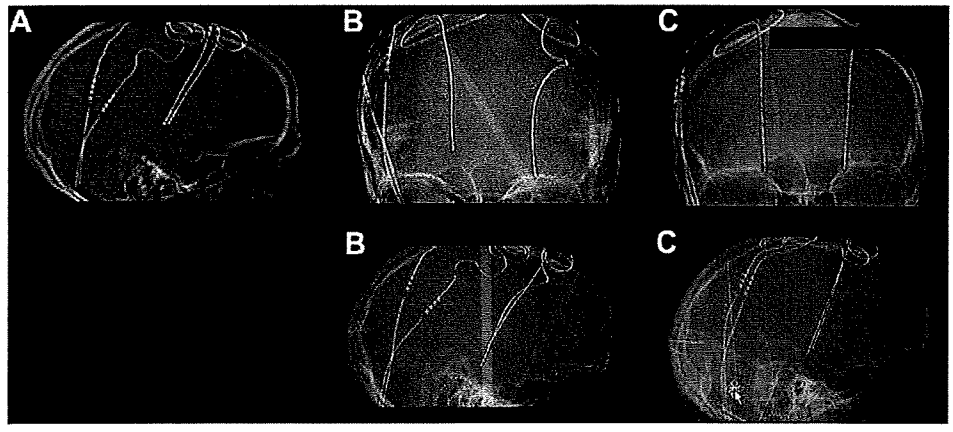

Fig. 7. Ventral lead migration shown by serial x-rays. A) A skull x-ray at one month post-implantation. B) A skull x-ray at fourteen months following first operation. The left and right leads had moved approximately 16 mm and 5 mm downwards from the initial position, respectively. C) A skull x-ray at one month following lead replacement.

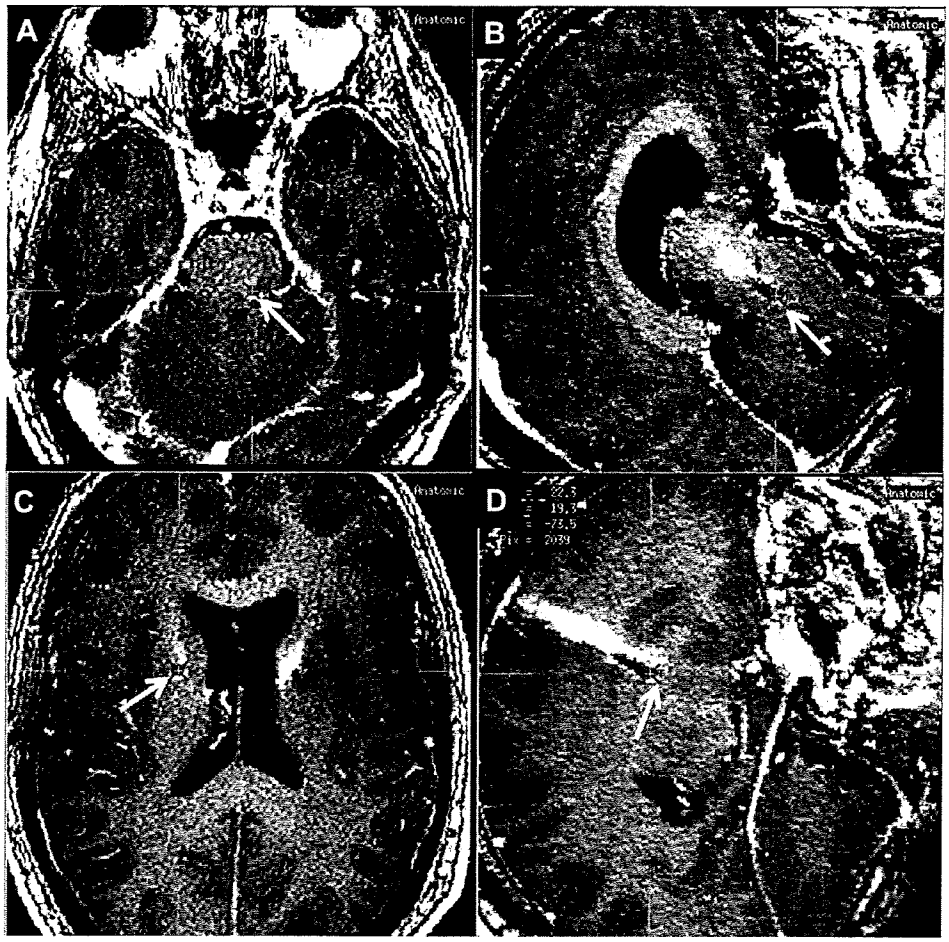

Fig. 8. Lead misplacement. Arrows indicate the tip of DBS leads. An axial slice (A) and a sagittal slice (B) of a T1 weighted magnetic resonance imaging (MRI) scan revealed the tip of the left DBS lead located too far posterior and deep for the subthalamic nucleus (STN). An axial slice (C) and a sagittal slice (D) of the same MRI scan revealed too shallow location of the left DBS lead.

(usually the result of a cerebrospinal fluid (CSF) leak [5]), and/or a failure in devices designed to secure the lead [49]. A suboptimal outcome from DBS surgery and/or low thresholds for stimulation-induced side effects (when the device is interrogated) may suggest lead misplacement. DBS leads placed in suboptimal locations may not be able to be corrected by programming [47]. Stimulation-induced side effects can lead to an urgent or an emergent situation, and in extreme cases can result in severe and sometimes unexpected symptoms. Even slight variations (sometimes only millimeters) of the location of a DBS lead may alleviate negative symptoms and lead to a more optimal therapeutic benefit [51] (Table 1).

2.3. Stimulation-related urgencies/emergencies

2.3.1. Stimulation-related motor symptoms

Stimulation-related motor symptoms include dyskinesia, chorea/ballism, gait disturbances, motor pulling, verbal fluency problems (verbal fluency has motor and non-motor/cognitive components), dysarthria, and hypophonia (Table 2). Many stimulation-induced motor symptoms resolve following reprogramming of the voltage, pulse width, and/or frequency.

If dyskinesia or chorea/ballism was induced by stimulation, reducing the amplitude/voltage of stimulation, or reducing the levodopa equivalent dose may alleviate the issue. Severe stimulation-induced dyskinesia/ballism in the clinic setting should alert the DBS programmer that voltage adjustment should be performed very slowly (sometimes in 0.1–0.2 V increment increases over many weeks). When stimulation-induced hyperkinesia is encountered, the ultimate outcome for patients is usually excellent. One important exception is underlying infection (e.g. pneumonia, UTI, etc.) which may exacerbate dyskinesia. We suggest an evaluation for an infectious process should be sought in cases where medical management proves difficult [18].

Although pre-existing gait and/or speech problems (e.g. on medication freezing, dysarthria, and hypophonia) do not typically respond to stimulation [23,52], stimulation-induced gait and speech issues may be improved in select cases with reprogramming, sometimes into a bipolar configuration. Patients themselves may discover relief by switching one or both devices (utilizing a remote control) to an off position when speaking. Additionally recent reports have revealed changing high frequency (>100 Hz) to lower frequency (<100 Hz) programming settings may improve gait, voice and other clinical features [53,54]. More research into DBS settings that may have the potential to improve or enhance clinical symptoms will be required, as some of the current low frequency settings seem to provide only temporary relief [53,54].

2.3.2. Stimulation-related non-motor symptoms

When stimulation spreads to surrounding neuronal regions, and to limbic and associative regions within grey matter structures, symptoms such as unpleasant feelings, paresthesias, behavioral complaints, and cognitive issues may emerge (Table 2). Pseudobulbar laughter and crying (mood incongruent) have been reported with stimulation, and both have been reportedly addressed by the use of antidepressant medications and by DBS reprogramming [55–57]. Two of the most worrisome stimulation-induced issues are depression and mania [32,58–62]. Both may require medication changes, reprogramming, verification of lead locations and potential hospitalization [47]. Depression should be carefully followed as it can result in suicidal ideation or suicidal attempt [32]. Several reports have linked stimulation of the substantia nigra region to acute depression in patients with STN DBS [58,59]. Abrupt cessation or reduction of dopaminergic medications can also result in apathy or depression [52,63]. If depression follows induction of stimulation, reprogramming to a more dorsal contact may be one solution. The lead location should be checked as misplacement into non-motor regions is one explanation for stimulation-induced non-motor features. Useful strategies include administration of antidepressants/antipsychotics, titrating neuropsychiatric medications to optimal doses, and completely optimizing dopaminergic medications [52]. Inpatient care including multi/interdisciplinary approaches (including psychiatrists, psychologists, neurologists, neurosurgeons and other health professionals) and behavioral therapies may also prove useful.

Table 2
Postoperative stimulation-induced urgencies and emergencies.

Issue	Routine/urgent/emergent	Management
Chorea/ballism	Routine/urgent	Try to program slowly (e.g. slow increase of voltage over many weeks/months). May try dorsal contact. May also reduce dopaminergic medications.
Dyskinesia	Routine/urgent	Reducing the dopaminergic medication may help. Try to program slowly (e.g. slow increase of voltage over many weeks/months). May try dorsal contact.
Motor pulling	Urgent	Try to reduce voltage or pulse width. Try bipolar stimulation, or possibly another lead contact. Some situations may require lead replacement. Check lead location.
Gait disturbance	Routine/urgent	Try another setting (e.g. another contact, reducing pulse width, voltage or frequency). Low frequency (60 Hz) with higher voltage or pulse width may help.
Verbal fluency problem	Routine	Try another contact, perhaps a more dorsal contact on the DBS lead. Try changing stimulation to bipolar or decrease pulse width, voltage or frequency.
Dysarthria/dysphagia	Routine	Try another contact. Try changing stimulation to bipolar or decrease pulse width, voltage or frequency. Check lead location. Prescribe speech therapy.
Hypophonia	Routine	Try another contact. Try changing stimulation to bipolar or decrease pulse width, voltage or frequency. Prescribe speech therapy.
Cognitive decline	Routine	This problem may be disease progression, surgery-related, or stimulation-related. Seek neuropsychological testing, consider reprogramming to a dorsal contact. Check lead location.
Mania/hypomania	Routine/urgent	Adjust medications. Consider discontinuation of dopamine agonist and use of quetiapine or clozapine. Consider moving to a dorsal contact and/or decreasing the pulse width, voltage or frequency. Check lead location. Consider admission for multi/interdisciplinary management.
Impulse control	Urgent	Adjust medications. Consider discontinuation of dopamine agonist and addition of clozaril or seroquel. Consider moving to a dorsal contact and/or decreasing the pulse width, voltage or frequency. Check lead location. Consider admission for multi/interdisciplinary management.
Suicide ideation/attempt	Emergent	Admit the patient to the hospital for multi/interdisciplinary care, and treat underlying cause. May need both medication adjustment and programming. Check lead location.
Anxiety/fear	Urgent	Consider more frequent and higher doses of dopaminergics, and altering DBS contacts, perhaps moving more dorsal. Check lead location. Consider admission for multi/interdisciplinary management.
Severe depression	Emergent	Behavioral therapy, counseling, medication adjustment and/or stimulation adjustment. Check lead location. Consider admission for multi/interdisciplinary management.
Postoperative mania	Urgent	Behavioral therapy, counseling, medication adjustment and/or stimulation adjustment. Check lead location. Consider admission for multi/interdisciplinary management.
Pseudobulbar cry/laughter	Urgent	SSRI, TCA or dextromethorphan.
Autonomic features	Urgent	May habituate on own, try stimulation parameter adjustments, or change contact if continues to be troublesome.
Sensory phenomena	Urgent	Try reduce voltage or pulse width. Try bipolar, or possibly other contact.
Accidental on/off	Urgent/emergent	Turn on the IPG, keep a diary to identify the problem.
Symptom rebound (motor and/or non-motor)	Emergent	DBS hardware workup including impedance check, battery check, x-ray study, and assess for tolerance.

2.3.3. Accidental on/off

When the DBS device unpredictably turns off, the clinician must investigate potential environmental triggers (the device has a duty log to assist in documenting these occurrences). Exposure to magnetic forces (e.g., a magnetized ice freezer or store security devices) is the most commonly reported etiology [47]. Prescribing "rechecking" of the DBS device on a regular or semi-regular schedule may prove useful (utilizing the patient issued remote control). Additionally, having the patient document and describe activities and relevant environments may yield the source of the problem. The patient should be educated to avoid strong magnetic fields, and to have their remote device with them at all times in order to recheck on/off status, and to learn prevention strategies for accidental on/off's. Most patients who undergo DBS surgery do not have any issues with accidental on/off's during the lifetime of their devices.

If more than one IPG is utilized to power multiple DBS leads, the chest pacemakers must be placed a minimum of six inches apart. Failure to separate the IPG's in space may result in cross-communication of the devices, and a result in an automatic and unintended reset to the factory default stimulation settings. We have observed this phenomenon in a single case, a boy with generalized dystonia and two chest IPGs (author observations). Interestingly when lying supine this boy's devices were six inches apart, but when leaning forward in a chair for programming sessions the distance was cut to only four inches. It is therefore important when programming to make sure (especially in children) that patients sit back in the chair, or alternatively lie in a supine position.

2.3.4. Symptom rebound

Several cases of severe symptom rebound following battery failure have been reported following DBS [64,65]. The more beneficial DBS is for clinical symptoms, the more dramatic the rebound symptoms may be. Symptom rebound may include both motor and non-motor manifestations such as tremor, gait problems, stiff legs and suicidal ideation (author observations), as well as severe depression. We have observed rebound of motor symptoms with battery failures in cases of dystonia and Parkinson's disease, but also rebound of non-motor symptoms including depression and suicidal ideation with battery failure (author observations). Sudden worsening of symptoms should always prompt a battery status check by an experienced DBS programmer. If the device is off, resuming stimulation may be all that is necessary (see Section 2.3.3). If the device is on, checking impedances and current drain at each of the four DBS contacts may provide useful information for evaluation of lead integrity (hardware malfunction) as discussed in the "hardware malfunction" section of this paper (Table 2).

3. Others

3.1. Dystonic storm

Dystonic storm or status dystonicus is a rare but possibly life-threatening condition which presents with severe generalized and possibly painful hyperkinetic dystonic spasms. Patients with an underlying history of primary or secondary dystonia are prone to this condition, and stressors such as trauma, infection or surgical intervention can trigger the dystonic spasms. The optimum treatment for this condition is not established, but a reasonable strategy is to use an aggressively increasing approach beginning with oral medications, then graduating to intravenous and intrathecal medications, then switching to deep sedation or anesthesia, and finally culminating with surgery [66]. Dopamine blockade with non-selective agents such as pimozide, risperidone, olanzapine or haloperidol and sedation with propofol and midazolam, have all been reported successful for the short term control of symptoms, and for improving quality of life. Manji et al. has reported that triple therapy with oral tetrabenazine, high-dose benzhexol, and pimozide is effective especially in children [67,68]. However, dystonic

storms may be unusually refractory to some oral medications. Patients with dystonic storms should be admitted to the intensive care unit (ICU) due to the possibility of accompanying respiratory compromise, hyperthermia, dehydration, and rhabdomyolysis resulting in potential renal failure. Deep sedation or anesthesia with endotracheal intubation may be required for refractory cases. Additionally, there has been at least one case of a patient with a dystonic storm successfully treated with intrathecal baclofen [69]. DBS or pallidotomy may be an option of last resort in cases where symptoms continue for many weeks/months [70,71]. Clinicians should be aware that postoperative infections and certain medications (dopamine blockers, antiemetics, etc.) can postoperatively induce movement disorders especially in patients with pre-existing basal ganglia damage.

4. Conclusion

Knowledge of potential DBS urgencies and emergencies can in many cases enhance outcomes. More intra- and postoperative urgencies and emergencies continue to be identified as the DBS field expands. Clinician's handling DBS in their practices should be versed in the identification and management of surgery/procedure related, hardware related, and stimulation-induced issues.

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BRAIN STIMULATION

RETROSPECTIVE STUDY

Impact of Subthalamic Nucleus Stimulation on Young-Onset Parkinson's Disease

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ABSTRACT

Objective. To clarify the efficacy of subthalamic nucleus (STN) stimulation in young-onset Parkinson's disease (PD), we compared the effects of STN stimulation on the motor symptoms between young-onset PD (YOPD) and late-onset PD (LOPD). **Methods.** We analyzed the effects of STN stimulation on motor function and motor fluctuations in 15 patients with YOPD, and 113 patients with LOPD who underwent STN stimulation during the same period. The Unified Parkinson's Disease Rating Scale (UPDRS) was evaluated during the on-period and off-period, which are defined as the times at which the motor symptoms are the best and worst during the daily active time with sustaining anti-parkinsonian drugs. The dyskinesia severity rating scale (DSRS) also was employed to assess the severity of peak-dose dyskinesia. We analyzed the changes in levodopa equivalent daily dose (LED), motor fluctuations, DSRS, and UPDRS part 3 score after STN stimulation, and compared the changes in each score between the two groups (YOPD vs. LOPD). **Results.** The LED was reduced, and the on-off motor fluctuation index, dyskinesia rating scale score (on-period), and UPDRS part 3 score (on- and off-periods) were improved in both the YOPD and LOPD groups. The improvement rates of the UPDRS part 3 scores in both the on- and off-periods in the YOPD group were superior to those in the LOPD group. The results of multivariate logistic regression analysis demonstrated that YOPD itself is the best responder to STN stimulation. **Conclusions.** STN stimulation can reduce the LED and improve motor fluctuations in patients with YOPD. The effects of STN stimulation on the motor symptoms of YOPD patients are superior to those in LOPD. The present findings suggest that YOPD patients suffering from several problems related to pharmacological therapy are probably good candidates for STN stimulation.

KEY WORDS: *Brain stimulation, neuromodulation, Parkinson's disease, subthalamic nucleus, young onset.*

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Introduction

The motor symptoms of Parkinson's disease (PD) commonly develop above the age of 50 years, with a mean age of onset of around 60 years (1). However, there is a group of patients in whom the motor symptoms of PD begin at a younger age. Such patients are designated as young-onset PD (YOPD), and their age of developing PD is between 21 and 40 years (2). YOPD patients display several clinical features which are different from those of patients who develop PD at above 40 years old (late-onset PD; LOPD). In comparison with LOPD patients, levodopa is more effective for YOPD patients, while patients with YOPD often experience treatment-induced motor complications, such as on-off motor fluctuations and dyskinesia which develop from the introduction of levodopa treatment in a short year (3–6). Many patients with YOPD therefore suffer from such motor complications of levodopa in the prime time of their life.

Stimulation of the subthalamic nucleus (STN) can ameliorate the on-off motor fluctuations and levodopa-induced dyskinesia (7–9). The effects of STN stimulation on the cardinal motor symptoms of PD are similar to those of a maximal dose of levodopa in each patient (8,10–12), and a presurgical good levodopa-reactivity in terms of motor disabilities is known to be a predictive factor for postsurgical improvement of motor function (9,13,14). Based on such clinical profiles of STN stimulation, YOPD patients can be regarded as the better candidates for STN stimulation therapy. However, although STN stimulation can improve the motor disability in patients with YOPD (15), it is not known whether the improvement effect of STN stimulation for YOPD patients is actually greater than that for LOPD patients. To clarify this issue, we examined the effects of STN stimulation on the motor symptoms of YOPD in comparison with LOPD.

Patients and Methods

Fifteen patients with YOPD underwent STN stimulation at our hospital (Itabashi Hospital, Nihon University School of Medicine) between October 2002 and August 2005. The characteristics of these YOPD patients are summarized in Table 1. We analyzed the effects of STN stimulation on motor function and motor fluctuations (i.e. on-off motor fluctuations and dyskinesia) in the YOPD patients preoperatively and at six months postoperatively. Furthermore, 113 non-YOPD patients who underwent STN stimulation during the same period also were analyzed for comparison with YOPD. Although the total 128 patients were clearly responsive to levodopa, their parkinsonian symptoms could not be controlled sufficiently with practically optimal pharmacological therapy. They also suffered from levodopa-induced side-effects, such as on-off motor fluctuations and dyskinesia. All patients underwent implantation of electrodes (model 3387; Medtronic, Inc., Minneapolis, MN, USA) and pulse generators for deep brain stimulation of the STN bilaterally. Preoperative and postoperative assessments of motor disability were performed using methods described in a previous publication (9). Briefly, the Unified Parkinson's Disease Rating Scale (UPDRS) (16) was evaluated during the on-period, which is defined as the time at which the motor symptoms are the best during the daily active time, and the off-period, which is defined the time at which the motor symptoms are the worst during the daily active time, with sustaining antiparkinsonian drugs. The preoperative characteristics of the two groups are summarized in Table 2. The preoperative mean levodopa equivalent daily dose (LED) (17) and UPDRS scores were not significantly different between the two groups (Table 2). The dyskinesia severity rating scale (DSRS) (18) was employed to assess the severity of peak-

TABLE 1. Characteristics of YOPD Patients

Patient	Sex	Age at onset (years)	Age at surgery (years)	Duration of PD (years)	Family history of PD
1	F	32	47	15	+*
2	M	30	44	14	–
3	F	34	42	8	–
4	M	34	42	8	–
5	M	39	52	13	–
6	F	31	49	18	–
7	F	23	53	30	–
8	F	39	62	23	–
9	M	35	55	20	–
10	M	38	66	28	+[i]
11	F	31	44	13	–
12	F	39	61	22	–
13	M	33	52	19	–
14	M	36	57	21	–
15	M	36	51	15	–

*Autosomal recessive juvenile PD; [i]sister is PD, mode of inheritance is unknown.
LOPD, late-onset PD; PD, Parkinson's disease; YOPD, young-onset PD.

TABLE 2. Patient Characteristics in the YOPD and LOPD Groups

Characteristic	YOPD	LOPD	*p* value
Sex (male, female)	8 M, 7 F	55 M, 58 F	
Age at onset (years)	34.0 ± 4.3	54.6 ± 6.9	<0.01
Age at surgery (years)	51.8 ± 7.4	64.4 ± 6.1	<0.01
Duration of PD (years)	17.8 ± 6.5	9.8 ± 4.9	<0.01
LED (mg/day)	641.0 ± 346.2	620.0 ± 316.9	NS
UPDRS part 2			
On-period	7.7 ± 5.9	9.9 ± 7.7	NS
Off-period	24.5 ± 9.2	22.1 ± 8.1	NS
UPDRS part 3			
On-period	22.8 ± 12.8	21.5 ± 13.3	NS
Off-period	43.6 ± 16.1	37.3 ± 13.8	NS
DSRS	12.9 ± 7.8	9.0 ± 6.7	NS
On-Off MF index	20.8 ± 15.1	15.8 ± 11.6	NS

DSRS, Dyskinesia Severity Rating Scale; LED, levodopa equivalent daily dose; LOPD, late-onset PD; MF, motor fluctuation; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young-onset PD.

dose dyskinesia, scoring the dyskinesia in six body parts (neck, trunk, and each of the four extremities) on a 5-point scale (ranging from 0 to 4, e.g., 0 = absent, 4 = severe). The incidence of peak-dose dyskinesia in the YOPD group (80.0%; 12 of 15 patients) was higher than that in the LOPD group (55.8%; 63 of 113 patients), whereas the DSRS score was not statistically significantly different between the two groups (Table 2). To estimate the severity of on-off motor fluctuations, we defined the score obtained by subtracting the UPDRS part 3 score at the off-period from the UPDRS part 3 score at the on-period as the "On-Off Motor Fluctuation Index." The presurgical On-Off Motor Fluctuation Index was not significantly different between the two groups. In order to exclude factors which could affect the motor activity, mini-mental status examination and Hamilton depression test were undertaken. The postsurgical stimulation parameters also were compared between the two groups.

Statistical Analysis

We compared each score for the YOPD group and LOPD group between before and after surgery, utilizing the Wilcoxon signed-rank test. We also compared the percentage reduction rate of LED (100 × [preoperative LED − postoperative LED]/preoperative LED) and the percentage improvement rates of the On-Off Motor Fluctuation Index, DSRS score, UPDRS part 2 and UPDRS part 3 scores (100 × [each preoperative score − each postoperative score]/each preoperative score) between the two groups employing the Mann–Whitney test. Multivariate logistic regression analysis was used to capture the common odds ratio between the postoperative improvement of the UPDRS part 3 score and various presurgical factors. Simple regression analysis was performed to assess the correlation of independent variables such as duration of disease and percentage improvement of motor score.

Results

We adjusted the stimulation parameters (intensity, frequency, pulse width, and contact) and levodopa so as to inhibit motor fluctuations and not to cause stimulation-induced side-effects (viz. spasticity, paresthesia, diplopia, dyskinesia, psychological symptoms, etc.) in each patient. No statistically significant difference in stimulation parameters between the two groups was evident at six months after chronic STN stimulation. Presurgical and six-month postsurgical examinations of both mood and cognitive function also revealed no significant differences between the two groups.

Changes in Motor Function, On-Off Motor Fluctuations, and ADL

The pre- and postoperative scores related to motor function in the on- and off-periods are shown in Table 3. In the YOPD group, the mean total motor score (UPDRS part 3) in both the on-period and off-period at six months after surgery were improved by bilateral STN stimulation (on-period, $p < 0.01$; off-period, $p < 0.01$; Table 3). The mean total motor score (UPDRS part 3) at six months after surgery in the LOPD group also was significantly reduced (on-period, $p < 0.01$; off-period, $p < 0.01$; Table 3). The percentage improvement rate of the motor score (UPDRS part 3) in each on- and off-period was significantly higher in the YOPD group ($p < 0.05$; Table 3).

The On-Off Motor Fluctuation Index was improved postoperatively in both groups ($p < 0.01$). While there was no significant difference in percentage improvement rate of the On-Off Motor Fluctuation Index between the two groups, the postoperative On-Off Motor Fluctuation Index was lower and the preoperative index was higher in the YOPD group as compared with the LOPD group. The results suggested that postsurgical improvement of on-off motor fluctuations showed a tendency to be prominent in patients with YOPD (Table 3).

Multivariate logistic regression analysis revealed preoperative predictive factors that contributed to postoperative improvement of the motor score (UPDRS part 3) in each on- and off-period (Table 4). An increased odds ratio was found in YOPD, but this association was statistically significant only for the on-period score (OR = 7.91; 95% CI, 0.84–48.1; $p < 0.05$). YOPD itself was the predictive factor that contributed to improvement of the total motor ability after STN stimulation during the on-period. A significantly decreased odds ratio was found for duration of disease during the on-period (OR = 0.92; 95% CI, 0.85–0.99; $p < 0.05$). Simple regression analysis revealed that there was a negative correlation between duration of disease and percentage improvement of the motor score (UPDRS part 3)

TABLE 3. Comparison of Preoperative Scores and Postoperative Scores in Patients With YOPD/LOPD

	YOPD (N = 15)			LOPD (N = 113)			
	Preoperative	Postoperative	% improvement	Preoperative	Postoperative	% improvement	p value*
LED (mg/day)	641.0 ± 346.2	498.0 ± 276.6	22[i]	620.0 ± 316.9	503.4 ± 256.6	19[i]	NS
UPDRS part 2							
On-period	7.7 ± 5.9	5.5 ± 4.5	28[i]	9.9 ± 7.7	7.8 ± 7.4	22[i]	NS
Off-period	24.5 ± 9.20	7.8 ± 4.20	68[i]	22.1 ± 8.20	11.6 ± 8.30	47[i]	<0.05
UPDRS part 3							
On-period	22.8 ± 12.8	12.9 ± 7.30	43[i]	21.5 ± 13.3	16.6 ± 12.0	23[i]	<0.05
Off-period	43.6 ± 16.1	16.8 ± 8.10	61[i]	37.3 ± 13.8	22.1 ± 13.4	41[i]	<0.01
DSRS	12.9 ± 7.80	3.9 ± 4.3	70[i]	9.0 ± 6.7	2.3 ± 3.7	74[i]	NS
On-Off MF index	20.8 ± 15.1	3.9 ± 4.8	81[i]	15.8 ± 11.6	5.5 ± 7.2	65[i]	NS

Values are expressed as the means ± SD. *percentage improvements after surgery are compared across the two groups. [i]$p < 0.05$ compared with preoperative scores. [i]$p < 0.01$ compared with preoperative scores.
DSRS, Dyskinesia Severity Rating Scale; LED, Levodopa equivalent daily dose; LOPD, late-onset PD; MF, motor fluctuation; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young-onset PD.

TABLE 4. Presurgical Factors for Postsurgical Improvement of the Total UPDRS Motor Score (part 3) in the On- and Off-Periods

Factors	Odds ratio (95% CI)	p value
On-period		
YOPD vs. LOPD	7.91 (1.30–48.1)	<0.05
Duration of PD	0.91 (0.84–0.99)	<0.05
Age at surgery	0.97 (0.91–1.03)	NS
Sex (male vs. female)	0.92 (0.44–1.90)	NS
Presurgical LED	0.79 (0.35–4.76)	NS
Off-period		
YOPD vs. LOPD	2.14 (0.39–11.7)	NS
Duration of PD	1.01 (0.94–1.09)	NS
Age at surgery	0.95 (0.90–1.01)	NS
Sex (male vs. female)	0.82 (0.40–1.68)	NS
Presurgical LED	0.92 (0.38–6.28)	NS

Multivariate logistic regression analysis showed that YOPD (age at onset <40 years old) significantly increased the odds ratio (OR) and duration of disease significantly decreased the OR for % improvement of the UPDRS part 3 score during the on-period. There was no significant between these factors but multivariate logistic regression analysis showed that YOPD (age at onset <40 years old) increased the odds ratio (OR) for % improvement of the UPDRS part 3 score during the off-period. A significantly decreased odds ratio was found for duration of disease during the on-period.
LED, levodopa equivalent daily dose; LOPD, late-onset PD; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young-onset PD.

during the on-period in the LOPD group ($r = -0.28$; $p < 0.01$; Fig. 1) while there was no correlation in the YOPD group ($r = 0.02$; $p = 0.96$; Fig. 1). It appeared that dopa-reactivity in YOPD may be maintained for longer than in LOPD, as the negative correlation between duration of disease and percentage improvement was significant in the LOPD group but not the YOPD group. In the present study, there is great difference between patient's number in YOPD group (N= 15) and that of LOPD group (N= 113). Thus, with the two groups combined, multivariate logistic regression analysis suggested therefore that duration of disease was a decreasing factor for the percentage improvement of the motor score (UPDRS part 3) during the on-period. Duration of disease was the predictive factor that impeded improvement of the total motor ability after STN stimulation during the on-period in LOPD particularly.

The mean activities of daily living (ADL) score (UPDRS part 2) at six months after surgery in both groups was significantly reduced (YOPD group, on-period, $p < 0.05$; off-period, $p < 0.01$; LOPD group, on-period, $p < 0.01$; off-period, $p < 0.01$; Table 3). The percentage improvement rate of the ADL score (UPDRS part 2) in the off-period was significantly higher in the YOPD group than in the LOPD group ($p < 0.05$), while there was no significant difference between the two groups in the on-period (Table 3).

Changes in Levodopa Equivalent Daily Dose and Dyskinesia

The LED was significantly reduced in both groups (21% reduction in the YOPD group, $p < 0.01$; 19% reduction in the LOPD group, $p < 0.01$; Table 3) at six months after surgery. The severity of peak-dose dyskinesia was significantly improved in both groups (69% improvement of the DSRS score in the YOPD group, $p < 0.01$; 74% improvement of the DSRS score in the LOPD group, $p < 0.01$; Table 3). There were no significant differences in both the percentage reduction of the LED and percentage improvement of the DSRS score between the two groups.

Discussion

Little information is yet available on the effects of STN stimulation in patients with YOPD. Only Krack et al. have

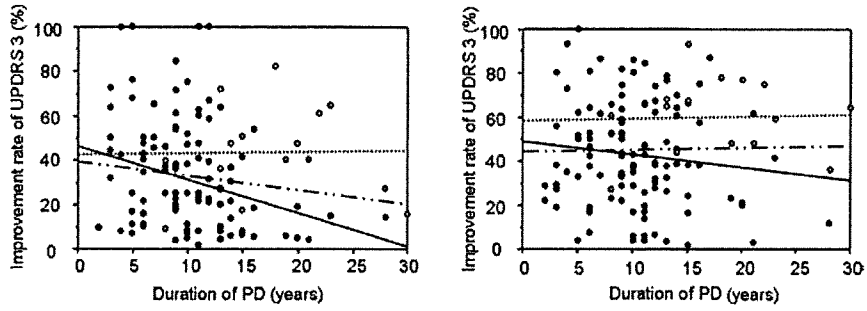

FIGURE 1. Correlations between improvement rate of Unified Parkinson's Disease Rating Scale (UPDRS) 3 and duration of disease during the on-period (left) and off-period (right). Simple regression analysis revealed a significant correlation in the late-onset PD (LOPD) group ($r = -0.28$, $p < 0.01$) but no significant correlation in the young-onset PD (YOPD) group ($r = -0.02$, $p = 0.96$) during the on-period. Open and solid circles represent YOPD patients and LOPD patients, respectively. The dotted and solid lines represent the regression lines for the YOPD group and LOPD group, respectively. The other (dot-dash) lines represent the regression lines for the two groups combined. There are some overlaps of data points. PD, Parkinson's disease.

reported in their comparative study (STN stimulation vs. globus pallidus stimulation) that STN stimulation can clearly ameliorate cardinal motor symptoms in patients with YOPD (15). In agreement with the findings of this earlier investigation by Krack et al. we confirmed that the total motor score (UPDRS part 3) in patients with YOPD could be effectively reduced by STN stimulation. In addition, the results of the present study showed that the impact of STN stimulation tends to be prominent in patients with YOPD rather than in patients with LOPD. Furthermore, the data of multivariate logistic regression analysis supported our assumption that YOPD itself is the best responder to STN stimulation.

We assume that the higher effectiveness of STN stimulation in YOPD patients may be related to the nonsignificant trend toward their high reactivity to levodopa. It is well-known that cardinal motor symptoms in YOPD patients commonly show a higher responsiveness to levodopa in comparison with those in LOPD patients (3–6). It also is evident that the effects of STN stimulation on parkinsonian motor symptoms are similar to those of levodopa (9), so that reactivity to STN stimulation could be greater in patients with YOPD than in patients with LOPD.

Another factor may be related to the characteristics of their unpleasant reactivity toward pharmacotherapy. YOPD patients often experience levodopa-induced motor complications, such as on-off motor fluctuations and dyskinesia, which frequently develop from the introduction of levodopa treatment in a short year (3–6). Although it was not significant, both dopa-induced dyskinesia and on-off motor fluctuations tended to be severe preoperatively in YOPD patients in comparison with LOPD patients in our study. Such motor complications can limit any increases in the levodopa dosage, so that pharmacotherapy is often restrained at a sub-maximal dose in these patients. STN stimulation can complement the potential of levodopa therapy without dopa-induced motor complications in patients taking a restrained dose of medication preoperatively.

Findings indicating that a younger age at surgery and shorter disease duration may be predictive of a better outcome have been reported (13,14). The data of multivariate logistic regression analysis obtained in the present study, showing a longer disease duration to be a negative predictive factor for a good outcome from surgery, supported such a view. However, our results of simple regression analysis suggested that the negative influence of a long duration of disease on postoperative improvement of motor function could be confirmed only in the LOPD group, and not in the YOPD group. One possible explanation for this is a difference in speed of disease progression: A good dopa-response was preserved in YOPD patients despite their longer disease duration. This finding could imply a better long-term outcome of STN stimulation in YOPD patients in comparison with LOPD patients.

It has been suggested that the introduction of levodopa therapy in patients with YOPD should be postponed for as long as possible, since YOPD patients tended to display a significantly higher frequency of both dopa-induced dyskinesia and on-off motor fluctuations, and such motor fluctuations can develop earlier than in LOPD patients (4,5,19–25). Initial single dopa-agonist therapy or combined dopa-agonist/low-dose levodopa therapy can significantly reduce the occurrence of dyskinesia due to subsequent levodopa therapy; however, 6–27% of patients have been reported to suffer from dopa-induced dyskinesia at three to five years after initiation of levodopa therapy (26–31). These findings highlight a remaining problem that many patients may still suffer from motor complications, such as on-off motor fluctuations and dyskinesia, at several years after successful

initial non-levodopa or low-dose levodopa with dopa-agonist therapy when maximal improvement in their motor function is achieved by such therapies in the earlier years. Furthermore, early introduction of levodopa therapy can improve motor function and quality of life to a greater extent than other anti-parkinsonian drugs, so that delayed introduction of levodopa therapy may impose a circumscribed life on some patients because of sub-maximal improvement in their motor function. The results of the present study suggest that YOPD patients with such problems related to pharmacological therapy probably represent good candidates for STN stimulation. Furthermore, early introduction of STN stimulation may preserve a better motor function and quality of life during the prime of their life. Although many authors have reported long-term effectiveness of STN stimulation for PD (32), the situation still remains uncertain in YOPD patients. One important issue to be resolved is therefore the long-term effect of STN stimulation in such patients.

Conclusion

The STN stimulation can reduce the LED, and improve both motor function and its fluctuations in patients with YOPD. These effects in YOPD patients are superior to those in LOPD patients. The present findings suggest that YOPD patients with several problems related to pharmacological therapy are probably good candidates for STN stimulation.

Conflict of Interest

The authors reported no conflict of interest.

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Comments

If they are perceptive, neurosurgeons who implant deep brain stimulation (DBS) systems for the treatment of Parkinson's disease (PD) will have noticed that certain subsets of patients seem to improve more than others. Patients with young-onset Parkinson's disease (YOPD) are often particularly good candidates for surgery. The majority of YOPD patients have a classical presentation of asymmetric tremor, rigidity, and bradykinesia which is highly levodopa-responsive, and they develop medication side effects quite early in the course of treatment compared to those patients whose Parkinson's symptoms occur later in life. In this important manuscript, Otaka et al. provide evidence that convincingly corroborates the clinical perception that YOPD patients respond better to DBS surgery.

Fifteen patients with YOPD who underwent DBS were compared with 113 patients suffering late-onset disease (LOPD) who had DBS procedures done during the same period. Scores on the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) were significantly improved in both groups, but in the YOPD group the reduction in "off-period" symptoms was 61% as compared to 41% in the LOPD group. In addition, improvement in "on-period" scores was significantly better in the YOPD than the LOPD patients. 41% improvement in the LOPD group is a bit less than in most published studies, which show an average improvement with DBS of approximately 60%. However, despite this modest improvement (or perhaps because of it), the investigators were able to demonstrate a statistically significant advantage of DBS for YOPD over LOPD.

This paper should be required reading for all neurologists and neurosurgeons evaluating patients with PD. The take-home message is that young-onset PD is a surgical disease and that DBS should be considered early, rather than late, in its clinical course.

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脳深部刺激装置

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要　旨
脳深部刺激装置には，implantable pulse generator（植込み型刺激装置）とlead（刺激電極）ならびに，これを接続するextension leadが含まれる．イメージ的には心臓ペースメーカーの刺激電極が脳内に存在する形になる．疼痛の治療に用いられる場合は，視床知覚中継核（視床Vc核）刺激が選択されることが多く，幻肢痛，神経根損傷など末梢神経の損傷後に出現する求心路遮断痛（神経障害性疼痛）に特に有効である．2本の刺激電極を用いるdual-lead刺激も開発され，治療成績も向上している．（ペインクリニック 30：167-174，2009）
キーワード：脳深部刺激療法，不随意運動，疼痛

1．脳深部刺激システム

脳深部刺激装置には，implantable pulse generator（植込み型刺激装置）とlead（刺激電極）ならびに，これを接続するextension leadが含まれる．細かい刺激条件の設定は，医師用のプログラマーを植込み型刺激装置の上に当て，経皮的に調整するが，患者用のプログラマーを用いて患者自身でも簡単な刺激の調整を行うことができる．

本邦では，植込み型刺激装置としてメドトロニック社製のSoletra®（アイトレルII）とITREL 3®が使用されている．アイトレルIIは不随意運動の治療に用いられ，ITREL3®は疼痛の治療に用いられることが多い．アイトレルIIは185 Hzまでの高頻度刺激が可能であるが，患者用プログラマーでは刺激のON/OFFのみが調整可能である．一方，ITREL 3®では高頻度刺激が130 Hzまでに制限されるが，痛みの治療に必要な刺激条件（刺激強度，刺激頻度，刺激幅）をあらかじめ設定した範囲内で，患者用プログラマーを用いて調整することができる．さらに，近年，脊髄刺激用に開発されたSynergy®刺激装置を用いれば，2本の刺激電極を1つの刺激装置と結線することができるので，電極間の刺激など新たな刺激方法を選択することができる．

刺激電極（DBSリード）の太さは1.27 mmで，先端が半球状になっている．通常使用されているDBSリードは，1.5 mmごとに1.5 mmの活性点が4個並んでいるが，0.5 mmごとに1.5 mmの活性点が4個並んでいるものも使用することができる（**図1**）．

〈Special Article〉 Treatment instruments for pain clinic
Deep brain stimulation system
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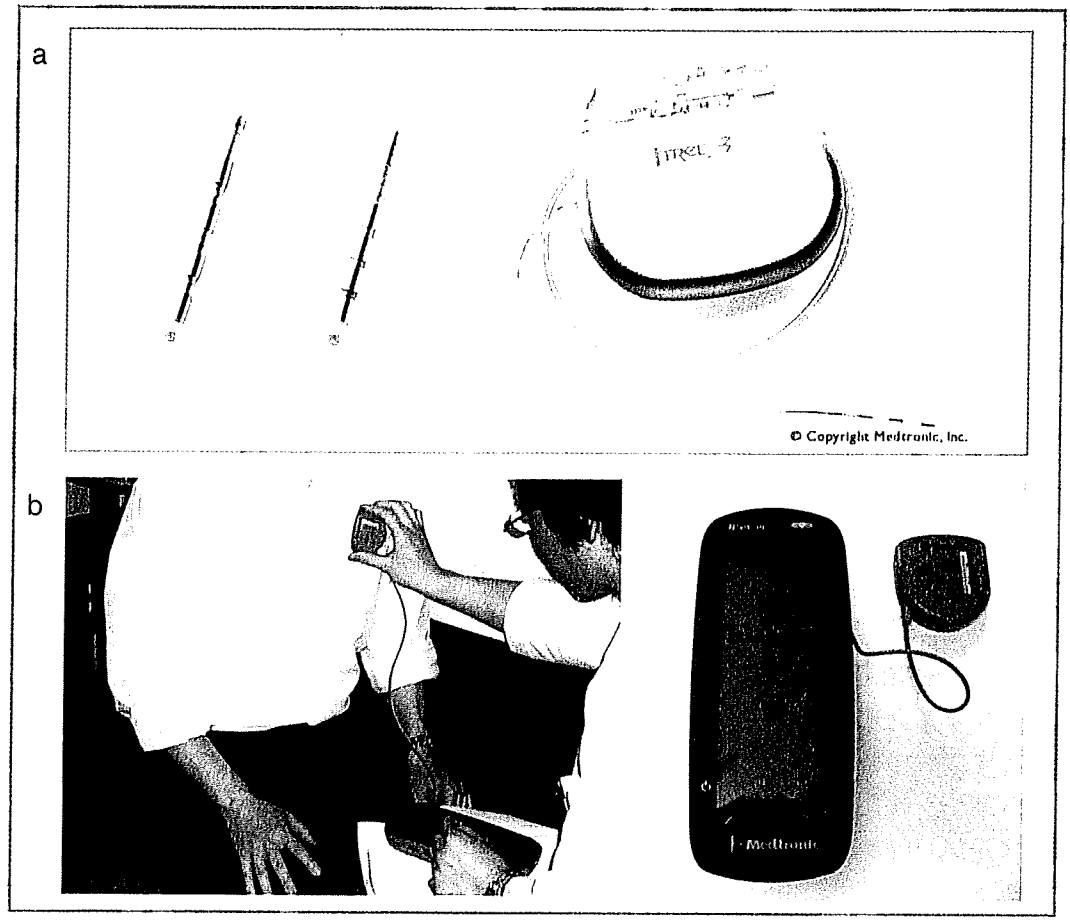

図 1　脳深部刺激装置
a：脳深部刺激電極（左）と慢性植込み型刺激装置.
b：医師用のプログラマー（N' VISION）を用いて刺激装置の条件設定を行っているところ（左）と N' VISION（右）

2．脳深部刺激の疼痛治療への応用

疼痛の治療を目的とした脳神経外科的方法としては，① 痛覚伝導路の破壊術，② 痛み抑制系の刺激療法，③ 疼痛を惹起する原因疾患に対する治療，に分けられる．痛覚伝導路を破壊する方法は，主としてがん性疼痛など，痛覚伝達系に過剰な信号が送られることによって出現する疼痛，すなわち侵害受容性疼痛（nociceptive pain）の治療に用いられてきた．しかし，経口オピオイド療法の開発や神経ブロック療法の進歩によって，侵害受容性疼痛の治療を目的とした神経伝導路の破壊術の頻度は激減している．一方，幻肢痛，神経根損傷後疼痛など，体性感覚系の求心路が損傷を受けた後に，二次的に出現する疼痛，すなわち神経障害性疼痛に対してはモルヒネや神経ブロックが無効であることが多いので，電気刺激療法が用いられることが多い．神経障害性疼痛には脊髄後根進入部破壊術の有効例も報告されている．しかし，痛覚伝導路を破壊する方法では，結果的に二次的な神経障害性疼痛を出現させる可能性があり，脊髄後根進入部破壊術もこの例外ではない．

中枢神経に損傷を有する神経障害性疼痛の代表的疾患は視床痛（thalamic pain）であり，Wal-