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Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

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A group of 37 patients diagnosed with Parkinson's disease (PD) were treated with subthalamic deep brain stimulation (STN DBS). The mean age at implantation was 59±11 years and PD has been present from 6 to 17 years (mean 9). The STN was identified by direct and indirect methods: macro stimulation and microrecording in all cases. At a three month follow-up, the authors observed a mean reduction of 49% in UPDRS II score and a mean reduction of 65% in UPDRS III score. Mean reduction of l-dopa consumption was 62%. The authors concluded that STN DBS safely reduces disabling symptoms of PD.

K e y w o r d s: deep brain stimulation, subthalamic nucleus, Parkinson's disease

1. Introduction

Since 1940s, neurosurgical treatment of Parkinson's disease (PD) has included three anatomical targets:

1) nucleus ventralis intermedius (Vim) of the thalamus, for tremor dominant PD, especially among elderly patients,
2) globus pallidus pars interna (GPi), for dyskinesia and dystonia dominant PD, especially when contralateral pallidotomy has been previously performed, and
3) subthalamic nucleus (STN), as the best target for a majority of PD patients for all l-dopa responsive symptoms.

STN is not the preferred option for patients with psychiatric symptoms and cognitive impairment.

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For the first forty years, neurosurgical treatment for PD consisted only of ablative procedures. However, since 1987, deep brain stimulation (DBS) has been included as a surgical tool in treatment of movement disorders. The DBS procedure has the advantage of reversibility and adjustability over time, as opposed to ablative procedures where the effects of the procedure are irreversible.

Introduction of the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model helped to identify STN as the optimal neurosurgical target. The subthalamic nucleus is believed to be the best anatomical target to alleviate the majority of PD motor symptoms that have responded to l-dopa prior to surgery. Surgical risk is similar for STN DBS and GPi or Vim DBS, but the advantages of STN DBS are marked. For example, STN DBS allows PD patients to reduce l-dopa consumption by 50–100%. The role of STN DBS in treatment of PD is well established and recognized as the best neurosurgical tool for selected groups of patients [1–11].

2. Materials and Methods

2.1. Patient Selection and Material

Twenty-three female and 14 male patients, with a mean age of 59 ± 11 years and PD histories of 6–17 years (mean 9 years) were qualified for surgery, according to the CAPSIT-PD criteria. All of the patients were examined by a neurologist specializing in movement disorders and by a functional neurosurgeon. The whole group of patients underwent brain MRI, neurological and neuropsychological evaluation prior to and after surgery. There were 35 patients who underwent the bilateral DBS STN implantation and two patients who underwent the unilateral STN DBS implantation. All pre-operative and post-operative evaluations were video recorded to allow for subsequent double blinded evaluation [12–18].

2.2. Surgical Procedure

A Leksell stereotactic frame was used in all cases for MRI guided identification of STN. All patients were taken off their Parkinson's medication for at least 24 hours prior to surgery and received a pre-operative antibiotic intravenously before transfer to the operating room. Target and entry points were identified and analysed with a neuronavigation system. The frame was attached to the patient's head after application of local anaesthetic. Pharmacological sedation was avoided so as not to interfere with surgeon-patient communication, which might affect intrasurgical monitoring. After a straight, 4 cm long skin incision had been marked over the coronal suture, centred 4 cm from the midline, the operative field was shaved, prepared, draped and infiltrated with local anaesthetic. A 14 mm burr-hole was made in the skull and the dura mater was opened, then the stereotactic arc was attached to the head ring. At that point, the surgeon introduced microelectrodes and began microrecording and macrostimulation.

During intra-operative stimulation, PD symptoms, e.g., rigidity, bradykinesia and tremor, were evaluated as well as adverse effects such as motor contractions, dysesthesia, and speech and cognitive dysfunctions. Once clinical improvement was identified without any occurrence of adverse effects, a control X-ray was taken and the probe was replaced by the definitive DBS electrode (3389-28, Medtronic, Minneapolis, MN). After the lateral control X-ray confirmed the location of the electrode as being identical to the probe, the electrode was anchored with a locking device (Stimlock, Medtronic, Minneapolis, MN) at the burr-hole and the scalp was closed. The stereotactic frame was then removed and the second stage of the procedure was performed under general anaesthesia. In the final step an internal pulse generator (Soletra, Medtronic, Minneapolis, MN) was connected to the electrode by an extension (7482-51 or 7482-95, Medtronic, Minneapolis, MN) and inserted in the chest or abdomen [19, 20].

2.3. Stimulation Parameters

The study group had deep brain stimulation initiated four weeks after the surgery. Initial parameters of the monopolar stimulation were set at a frequency between130 and 185 Hz, a pulse width from 60 to 210 μs, and mean amplitude of 2.0 V. The parameters were readjusted over time according to the clinical effect determined at follow up. If needed, bipolar stimulation was replaced with monopolar. The goals for programming were to optimize clinical benefits while minimizing adverse effects and current consumption. Adverse side effects from overstimulation of STN, or stimulation of surrounding structures, might include: dyskinesia, pseudodystonia, dysarthria, eyelid opening apraxia, ocular deviation, ipsilateral mydriasis, ipsilateral perspiration, contralateral paresthesias, akinesia hemibalism, suicidal ideation, depression or manic behaviour. All such symptoms were well controlled by reprogramming the stimulation parameters [1, 21–24].

3. Results

3.1. Benefits and Adverse Events

At the 12-month follow-up, there was a 49% mean reduction in the UPDRS II score and a 65% mean reduction in the UPDRS III score in the study group. Mean L-dopa consumption decreased by 62% on average, (20–100%).

A few adverse effects were associated with the surgery. One CT scan identified an intracerebral haemorrhage that did not cause any neurological deterioration. The haematoma vanished one week after the surgery as recorded by the control CT-scan (1/72 implantation-1.4%). Three chest haematomas were noticed around the internal pulse generator, which were treated conservatively (3/72–4.2%). The family of one subject reported a hypomanic behaviour that went unnoticed by the patient himself

(1/37patients–2.7%). This hypomanic behaviour vanished after reducing the DBS voltage. The occurrence of infection forced the authors to remove unilaterally one whole system two months after implantation. Three months later, after antibiotic treatment, the system was re-implanted successfully (1.4%). One patient deteriorated cognitively after the surgery (1/37–2.7%), however, this and other side effects related to the stimulation were always reversible. The stimulation parameters were readjusted so that mild side effects were tolerable for the patients, who otherwise enjoyed good or excellent outcomes with regard to motor symptoms. There was no mortality within the group.

4. Discussion

4.1. Functional Neurosurgery in Movement Disorders

Functional neurosurgery is strongly associated with the development of stereotactic neurosurgery. Broca (1868), Zernov (1889) and Rossolimo (1900) developed stereotactic frames that were used only for non-clinical purposes. The apparatus developed by Horsley and Clarke (1906) was first used in humans by Mussen and Kirschner (1933) who penetrated the foramen ovale while treating trigeminal neuralgia. Spiegel and Wycis used the Horsley-Clarke frame for ablation of basal ganglia in 1947; this may be regarded as the beginning of the new subspecialty of functional and stereotactic neurosurgery. These last authors noticed that stimulation of the target point before ablation with a high frequency current (above 100 Hz) caused reversible clinical improvement. Most of the later surgeons used intrasurgical stimulation prior to ablation in order to predict clinical improvement.

Rapid development of the new technique was followed by modernization and the introduction of new stereotactic frames by Talairach, Leksell, and others. Although introduction of more sophisticated stereotactic frames improved the accuracy of the method, the mode of treatment did not change—Technical limitations did not allow widespread use of the deep brain stimulation, and the ablative technique remained the only surgical option for movement disorders treatment for several decades.

The main advantage of ablative techniques is the fact that the procedure is short and inexpensive. However, a huge disadvantage of pallidotomies or thalamotomies is the fact that the effects of these procedures, which include adverse events, are irreversible. Another disadvantage of the ablative procedure in general is that it precludes any subsequent neurosurgical intervention like deep brain stimulation (DBS), grafting or gene therapies for those patients. As well, when the disease progresses or the clinical effects of ablative surgery are insufficient, as in the majority of patients, the ablative procedure does not allow the repetition of surgery [1, 2, 5, 9–11, 25].

After 1948, a series of trials were performed utilising deep brain stimulation to treat depression or pain, but technical limitations did not allow those procedures to be popularised until 1980s. The appearance of new hardware allowed the rapid

introduction of DBS in the following new clinical indications: essential tremor (FDA approved 1997), Parkinson's disease (FDA approved 2002), and dystonia (FDA approved 2003). The great advantage of DBS is its low destructive effect on surrounding tissues, which is limited only to structures in active contact with the electrodes.

The DBS mechanism is unclear. One suggestion is that DBS blocks neuronal transmission through inactivation of voltage-dependent channels. Another is that it provides antidromic stimulation of inhibitory afferents to the target nucleus and the local release of GABA. A third possibility is that DBS masks encoded information by superimposing nonphysiologic, high-frequency patterns, which would either activate local inhibitory circuits within the target structure or harmonize with basal ganglia circuits (gamma activity 70 Hz).

The pathophysiological model of STN DBS is complex as well, and may be explained by several theories: a blockage of the abnormal neuronal activity at the level of STN, inhibition of GPi and SNr by direct suppression, or antidromic increase of GABA activity in GPe (SNr and GPi). Probably each of these theories has some role in the treatment, making it difficult for researchers to identify which is the most important [17, 26, 28, 29].

Effects of DBS STN on the quality of life of patients, and of caregivers, the reduction in dyskinesia and l-dopa consumption, and changes reflected by the UPDRS part III (Unified Parkinson Disease Rating Scale) have been widely elaborated upon by other studies.

Successful treatment depends on a number of factors: optimal candidate selection, optimal target selection, electrode positioning, DBS programming, medication management and appropriate patient follow up. Appropriate patient selection plays a key role in a successful outcome; the criteria include age, diagnosis, history and severity of PD, and other physical and psychological health conditions. Patients with non-idiopathic parkinsonism are poor candidates, as they are patients of advanced age. While good candidates have had PD for at least five years, treatment of patients with a history of PD longer than fifteen years yields poorer results. The optimal clinical state of PD patients qualified for STN DBS is grade III according to the Hoehn Yahr scale. Response to l-dopa is a key factor; good responders to l-dopa are also good responders to STN DBS. STN DBS has an effect on motor symptoms of PD that respond to l-dopa treatment: bradykinesia, tremor, rigidity, dystonic movements and postures, motor fluctuations and dyskinesias.

STN DBS has no effect on autonomic dysfunction, psychiatric impairment and cognitive decline. Any psychiatric or cognitive impairment present prior to implantation tends to deteriorate after surgery.

During the qualification process, UPDRS III "off" should be at least 40 of 108. A lower UPDRS score can be accepted in cases of: severe tremor-predominant PD, severe gait impairment, disabling dystonia or dyskinesia, medication intolerance, and prominent fluctuations and dose failures. A good prognostic factor is the difference between UPDS III "on" and "off", which should be at least 30% [30–33].

Neuropsychological evaluation plays an important role in the qualification process leading to the surgery since cognitive impairment is the most common cause for exclusion from the STN DBS treatment. Cognitive deterioration has been observed after STN DBS in elderly patients with and without pre-existing cognitive impairment and in patients with pre-existing executive dysfunction. The most consistent cognitive side effects after STN DBS are a decrease in word fluency, verbal memory, visospatial memory and working memory. Transient depression has also been observed in 25% of the patients after implantation of DBS, while reports of hypomanic behaviour are not infrequent. Drug-induced hallucinations have not been identified as contra-indicative for STN DBS, however delusions associated with paranoia usually imply dementia, and those candidates should not be accepted for surgery.

Contraindications to surgery for the DBS implantation include: coagulopathies, severe uncontrolled hypertension, cerebrovascular disease, severe coronary heart disease, terminal state, cardiac pacemaker, and psychiatric disorders [22, 23].

A complete DBS team should consist of a movement disorders neurologist, functional neurosurgeon, neurophysiologist, neuropsychologist, neuroradiologist, physiotherapist, occupational therapist, and speech therapist. Strict, constant and direct cooperation between members of the DBS team at all levels, in the qualification process, surgical treatment, perioperative care and follow up, is key to the success of treatment [10, 21, 23, 34].

4.2. Advantages and Disadvantages of DBS

Although some complications of DBS, primarily related to the current technology, can be viewed as disadvantages, they seem to be minimal so far. We can not yet know whether implantation and DBS may result in the DBS-dependency similar to the shunt dependency observed among hydrocephalic patients. Nor do we know whether battery failure, (possibly every one to five years) may lead to a severe clinical deterioration. Hardware-related complications observed in our study include the risk of infection, migration of leads or internal pulse generators, as well as lead fractures. It may also be problematic for patients to have frequent and time consuming adjustments to stimulation, especially for those who live at a distance from the specialized medical centres.

DBS may restrict other treatments. For example, monopolar diathermy and exposure to strong magnetic fields should be avoided. Finally, price may be an important issue for some insurance programs.

The great advantage of DBS is its reversibility. This mode of treatment does not require any destructive lesion of the brain, and consequently results in fewer adverse events in comparison to ablation. The stimulation can be adjusted and readjusted postoperatively to improve its efficacy or to reduce adverse effects. As well, the efficacy of DBS is a suitable candidate for double-blinded study, which is impossible after

ablative procedures. Because of its reversible nature, DBS preserves future options for patients in the event that new, more effective therapy emerges, such as fetal cell transplantation and gene therapy [1, 2, 4, 6, 31, 33, 34].

5. Conclusions

Subthalamic deep brain stimulation remains the best option for neurosurgical treatment of Parkinson's disease in a selected group of patients. Appropriate selection, accurate electrode placement and skilled surgical care are the key factors in the effective treatment. A DBS-dedicated movement disorder team should contain a neurologist, stereotactic neurosurgeon, neurophysiologist, neuropsychologist and therapists who would be able to cover pre-surgical qualification and post-surgical follow-up of patients.

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