Deep Brain Stimulation: An Evolving Technology to Treat Parkinson’s Disease, Dystonia and Essential Tremor

Experience at Texas Tech Clinic, El Paso

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ABSTRACT
Deep brain stimulation (DBS) has gained widespread popularity as a surgical treatment for medically refractory symptoms of Parkinson’s disease, essential tremor and dystonia. Dyskinesias from levodopa also are totally controlled with DBS. We wish to report the summative clinical results of high-frequency DBS performed in patients of the Movement Disorder Clinic at Texas Tech University in El Paso selected for DBS treatment because of medically refractory Parkinson’s disease and its motor fluctuation, and because of essential tremor and dystonia refractory to medical treatment.

ABBREVIATIONS
Deep brain stimulation (DBS)
Parkinson’s disease (PD)
Essential tremor (ET)
Subthalamic nucleus (STN)
Ventral intermediate (VIM)
Globus pallidus internus (Gpi)
Implantable pulse generator (IPG)
Unified Parkinson’s Disease Rating Scale (UPDRS)

KEY WORDS
Deep brain stimulation
Parkinson disease
Essential tremor
Dystonia

INTRODUCTION
Deep brain stimulation (DBS) is an approved and effective treatment for medically refractory Parkinson’s disease (PD), essential tremor (ET), refractory dystonia and obsessive compulsive disorder. DBS comprises the implantation of electrodes deep in the subcortical regions of the brain to stimulate specific structures. Each electrode has multiple contacts that lie at different depths, allowing options for stimulating at different levels along the electrode trajectory. On a second surgical intervention one week after the insertion of the electrodes, these electrodes are connected by a subcutaneous wire to an implantable pulse generator (IPG) that contains the electrical generator and a 3 V battery. The IPG is capable of multiple possible current configurations by alterations of current frequency, pulse width and amplitude. The high-frequency stimulation supposedly inhibits target regions in the brain and isolates that region from the electrical circuitry that it belongs. In this regard DBS has the effects of ablation but it has the advantage of being reversible.

We wish to report the clinical results of high-frequency DBS performed in patients of the Movement Disorder Clinic at Texas Tech University in El Paso, who were selected for DBS treatment because of medically refractory PD and its motor fluctuations; and because of ET and dystonia refractory to medical treatment.

METHODS
From 2000 to 2013 a total of 55 patients ages from 32 to 79 years underwent DBS surgery. PD accounted for 46 patients, 38 males and 8 females and on average they had suffered symptoms for 18 years.

Of the seven patients who had ET, 2 were males and 5 were females. Two female patients with dystonia underwent DBS surgery. Of the two patients with dystonia, one had dystonic type of cerebral palsy and the other one primary dystonia with positive DYT1 DNA test.

All PD patients had bilateral DBS electrode insertion in the subthalamic nucleus (STN). The target for ET was the ventral intermediate (VIM) nucleus of the thalamus; and with one exception, all had bilateral insertion of electrodes. The two patients with dystonia had bilateral globus pallidus internus (Gpi) electrode insertion.

With the exception of three patients operated outside El Paso, and three patients operated at the University Medical Center of El Paso, Texas, all other patients were intervened at Sierra Medical Center of El Paso, Texas by Drs. David Masel, Daniel Lacerte and Fadi Hanbali.

In the last 3 years the frameless neuro-navigation deep brain stimulation surgery replaced the frame-based stereotactic surgical implantation of intracerebral electrodes. This innovation simplified the surgical procedure by shortening the operative time from more than 5 hours to less than 2 hours. This manifested itself as more comfort to the patient who is supposed to be awake and interacting with the neurosurgeon and the neurologist through the whole surgical procedure. It also provided better accuracy in target acquisition and lead implantation.

The life of the IPG battery lasted from two to 7 years depending on the settings and on the use of the IPG. An increase of voltage over 4 V, drained the battery in less than two years. This

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occurred in one patient with dystonia, who finally had a rechargeable battery when it became commercially available. Turning the battery off at night extended the life of the battery. The replacement of the battery is done on an outpatient basis and is performed with intravenous sedation.

INDICATIONS FOR SURGERY
Conventional inclusion criteria were used. All patients with idiopathic Parkinson disease had responded to treatment with levodopa-carbidopa, and combinations with entacapone, dopamine agonists, and MAO type-B inhibitors. However, after several years of treatment their quality of life was drastically affected because of the development of severe motor complications with on-off fluctuations and disabling dyskinesias which were present more than 50 per cent of the time. All patients with ET had constant, large amplitude medication-refractory head and limb tremor affecting activities of daily living. Two Patients with ET also had voice tremor. The patient with positive DYT1 dystonia had primary torsion dystonia and had been totally incapacitated and crippled. At age 15 she underwent bilateral pallidotomy which helped little. At age 21 (in 2003) she had bilateral Gpi electrode implants for DBS. The other dystonic patient was a 32-year-old woman with spas tic/dystonic quadriplegic cerebral palsy who had many cor rective surgeries and a Baclofen pump to relieve the spastic dys tonic symptoms. In this patient, bilateral Gpi electrode insertion for DBS was performed to facilitate management.

All patients were categorized as severely or extremely ill before the surgery. All patients were appropriate candidates for surgical procedures. All had normal or near normal cognitive function and they understood the nature of the DBS therapy and were available for frequent follow-up visits.

Patients with Parkinson’s disease continue to take medications as they did prior to the surgery. They were instructed to understand that reduction of medication was not the ultimate goal of DBS therapy. Ideally, it was expected a balance between surgery and medication and that the dose of medicine had to be adjusted as necessary as the stimulation therapy was maximized.

ADVERSE EFFECT OF SURGERY
There were no complications related to intracranial hemorrhage or hardware implant. One patient had a tonic-clonic generalized seizure 6 months after the DBS implant. Seizure did not recur and antiepileptic medication was continued. In one patient the hardware was removed because of infection in the IPG and the connection wiring.

FOLLOW-UP
Initial program was performed 3 days after the IPG implant. Patients were followed weekly for 4 weeks, monthly for two months and every three months thereafter. The current pulse frequency of the IPG ranged from 180 to 220 Hz, the pulse width from 90 to 240 microseconds, and the amplitude from 3 to 4.5 volts.

Visits as frequent as once a week were necessary during the first months to maximize the benefit of the stimulation therapy. Once stimulation was maximized, patients returned every 3 months.

The Unified Parkinson’s disease Rating Scale (UPDRS) was used in every visit before and after surgery to assess and follow the course of PD before and after STN, Gpi, and VIM thalamic deep brain stimulation. The clinical assessment included behavior, mood, and activities of daily living, motor abilities and adverse effect of treatments.

The UPDRS was applied by the same healthcare professional and points were assigned to every item based upon the individual’s response, as well as observation and physical examination. Parts I, II, and III contain 44 questions, and each item is measured on a five-point scale, while part IV contains 11 questions with the scale ranging from 0 to 23. The final cumulative score will range from 0 (no disability) to 199 (total disability). Part IV evaluates complication of levodopa treatment.

Clinical meaningful changes in PD progression and response to DBS therapy were measured according to the flowing reasonable estimates (Shulman): UPSRS changes for total score was 4 points for minimal changes, 9 points for moderate changes and 17 points for large changes.

UPDRS changes for motor score was 2.5 points for minimal changes, 5 points for moderate changes and 11 points for large changes. This was assessed according to the following estimates: 1 to 10 points represents early illness; 11 to 20 points represents moderate illness; and more than 21 points represents advanced illness.

Part I appraises cognitive function, thought content, behavior, initiative, and mood.

No changes were observed in cognitive function. One patient had delusional thinking 6 month after surgery. Upon concern of his primary care physician the stimulation was turned off temporarily but he continued to have delusions which resolved with antipsychotic treatments. Motivation and initiative improved and this was attributed to the fact that patients were more functional in other aspect of their activities.

Part II is a self-evaluation of the activities of daily life: speech, salivation, swallowing, handwriting, cutting food, dressing, hygiene, turning in bed, falling, freezing, walking, tremor and sensory difficulties.

The self-assessment showed significant improvement. Improvement of tremor was greater than 80% and in patients with ET was totally controlled. Activities of daily living such as dressing, ability to maintain hygiene, eating and handwriting slowly took a favorable turn towards an independent life with significant reductions in the numbers of the UPDRS scale. There was an increase in the number of falls because the patients were more active after the DBS implant than before surgery. In one patient with ET who also had voice tremor speech fluency and voice shuddering worsened after DBS with IPG settings necessary to control the limb tremor.

Part III evaluation of motor function: speech, facial expression, tremor at rest, action tremor, rigidity, finger taps, hand move-

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Motor function showed a more meaningful improvement than in the other sections of the UPDRS scale. Numbers were reduced from severe disease to moderate disease. Most patients with PD had an improvement in motor UPDRS greater than 30%. Tremor of Parkinson’s disease and of essential tremor improved almost immediately at the clinic when the IPG program was maximized. Dystonia, rigidity and dyskinesia took several weeks for maximal response. The patient with primary dystonia was able to walk erect and without assistance. She was able to attend college. Her neck and facial and pharyngeal dystonia persisted. No functional gain was achieved in the other dystonic patient with cerebral palsy.

Part IV evaluation of complications of therapy: Dyskinesia, early morning dystonia, "off-period" deterioration, including the duration of "off" periods, predictability based on dosage, and whether onset of off periods is sudden or gradual; anorexia (including nausea and/or vomiting), sleep disturbance, and symptomatic orthostasis.

Dyskinesias and dystonic postures were totally controlled in most PD patients. There were no changes in orthostatic symptoms and in sleep disturbances. A reduction of the dose of levodopa was not the ultimate goal, but half of the patients were able to reduce the dose of levodopa. Dopamine agonists were not changed.

Two more scales used in the evaluation are not part of the UPDRS:

Hoehn and Yahr scale staging shows the severity of Parkinson’s disease: This scale goes from Stage 0 = no signs of disease, to Stage 5 = Wheelchair bound or bedridden.

Evaluation: 80% of patients improved two points in the Hoehn and Yahr scale

Schwab and England Activities of Daily Living Scale states the percentage of independence from 100% independent to 0% independent. Evaluation: Five patients returned to work or to school; and in 80% of patients there was positive improvement regarding patients’ independent state. After 12 months of DBS, over 80 percent of the patients experienced improvement and none of the patients were rated as severely or extremely ill.

Four patients died in the 13-year follow up period unrelated to surgery due to complication of comorbidities.

DISCUSSION
Parkinson’s disease is the clinical expression of a mixed pathology of polyproteinopathies. Abnormal proteins, such as mutations of α-synuclein, TAU, and progranulin converge to produce a spectrum of clinical syndromes that fade into each other like the colors of the rainbow; from the unique idiopathic Parkinson’s disease, through Parkinsonism plus Alzheimers disease, Parkinsonism plus psychosis (Lewy body dementia), Parkinsonism with dysautonomia (multiple system atrophy), Parkinsonism with motor neuron disease, Parkinsonism with proprioceptive changes (cortico-basal-ganglionic degeneration) to Parkinsonism plus suprabulbar palsy (Richardson, Steel, Olszewski syndrome).

Of all these Parkinsonism syndromes only idiopathic Parkinson disease is responsive to treatment with levodopa. After several years of responsiveness to levodopa the striatal neurons began to show the effect of their progressive denervation hypersensitivity and they exhibit an erratic response to the exogenous dopamine. This erratic, unpredictable reaction is clinically manifested by a disabling motor fluctuation varying from dyskinesias (chorea produced by levodopa) to total freezing.

Deep brain stimulation ameliorates all the motor syndromes that are improved by levodopa and totally controls the dyskinesias produced by levodopa. The most important point to remember when considering the referral of a patient is that only those symptoms that respond to levodopa will respond to DBS.

DBS should be reserved for levodopa-responsive symptoms in non-demented patients with PD who may also have troublesome tremor or on-off motor fluctuations. DBS is also very effective for ET and dystonia. The STN remains the most widely used target for DBS in PD. The thalamic target (VIM) is effective for essential tremor and the STN and GPi targets are used for dystonia.

We have presented here a small group of patients from El Paso community with PD, ET and dystonia, who were selected for DBS because they fulfilled the criteria to be considered for DBS surgery. It is expected that in the future as the medical school and the local hospitals become part of a larger consortium in movement disorder the number of patients referred to surgery will increase.

Careful attention should be paid to patient selection, monitoring and management. New hardware, batteries with a long life and increased programming options will be among the many challenges facing DBS in years to come.

REFERENCES

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