Is Deep Brain Stimulation a Viable Treatment for Parkinson's Disease?

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Abstract
Treatment options for those suffering from Parkinson's Disease are as diverse as its symptoms. With the advent of modern technology there are new and innovative treatments that are becoming available, such as Deep Brain Stimulation (DBS). Prior to exploring treatment options one must t understand the various causes of the disease. Treatment of the various motor and non-motor symptoms can include a combination of medication and surgical therapies. Among surgical interventions DBS is the treatment of choice. It has the fewest side effects and provides the greatest symptomatic relief.

Introduction
Parkinson's disease was first formally written about in 1817, by a prestigious English doctor, James Parkinson. He published a short pamphlet about the disease titled, "An Essay on Shaking Palsy". In the beginning of his paper he describes the symptoms of the disease as "involuntary tremulous motion, with lessened muscular power parts not in action and even when supported; with a propensity to bend, with trunk forwards and to pass from a walking to running pace; the senses and intellect being uninjured". (Elis, 2013) Parkinson was not the one who discovered the disease as there are sources referencing the disease dating back to the ancient Egypt and Mesopotamia. (Raudino, 2012) As time, technology, and science advanced, scientists and medical professionals were able to further understand the causes and symptoms of the disease. Treatment options for those suffering from Parkinson's are as diverse as its symptoms. With the advent of modern technology, there are new and innovative treatments that are becoming available. One of these new treatments is Deep Brain Stimulation (DBS). As with all new treatments, one has to assess its effectiveness, its side effects and how it compares with old methods of treatment. This paper will address these issues in relation to DBS and its treatment for Parkinson's disease.

Methods
This systematic review was composed after reviewing relevant journal articles about the subject matter. Articles used discussed causes of the disease, current treatment methods and alternative surgical interventions. Articles were obtained using search engines like Proquest and MedLine and articles from published journals.

Background
Prior to exploring treatment options, one must thoroughly understand the disease and its causes. Parkinson's has many different causes, some rooted in genetics, others in chemical imbalances. The genetic cause for this disease has been shown to include five different genes. (Pchelina, et. al. 2014) The first of these genetic proteins is α-synuclein, a neuronal protein which serves an unknown function. These proteins aggregate in the Lewy bodies, causing researchers to conclude that they play a major role in the protein composition of the Lewy bodies. Although mutations within α-synuclein are relatively rare; even patients with sporadic PD seem to exhibit protein aggregates in the Lewy bodies, leading researchers to believe that α-synuclein plays a major role in both genetic and sporadic forms of PD. Several independent family studies done on groups of people with PD show that α-synuclein mutations are a rare cause of PD. The largest analyses done on α-synuclein and PD indicated that allele length variability is associated with an increased risk for PD. (Pihlstrøm, Toft, 2011).

Mutations in the gene encoding parkin, a 465 amino acid chain protein is one of the causes of autosomal recessive PD. Parkin mutations in familial PD suggest that the ubiquitin-protease system has an important role in the disease. (Pickrel, Youle, 2015)

Mitochondrial abnormalities are also thought to cause the disease. These abnormalities lead to a failure of cellular energy production and increased free radicals. The newest gene discovered which confirmed these hypotheses is the PINK1 gene. (Pickrel, Youle, 2015).

Another gene associated with Parkinson's is the DJ-1 protein. Although its exact function is unknown, it is thought to help with proper protein folding. DJ-1 protein may be linked to abnormalities in the protein control system. Other studies show that DJ-1 mutations may lead to increased levels of oxidative stress. (Pchelina, et. al. 2014).

PD is not caused by genetic factors, although genetic factors increase one's risk for developing the disorder. Sporadic PD is when there are multiple genetic alterations which increase the risk of developing PD, but they do not cause PD. One such risk factor is prevalent among Ashkenazi Jews carrying the GBA gene mutation. Those who do have a GBA mutation are seven times more likely to develop the disease when compared to healthy control groups. (Feany, 2004).

The most common cause for PD is from the progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Motor symptoms appear when approximately 50%–60% of these neurons degenerate, causing a 70%–80% depletion of dopamine levels in the dorsal striatum. (Pickrel, Youle, 2015).

Discussion

Parkinson's disease is associated with a wide variety of symptoms, both motor and non-motor. The four cardinal motor symptoms associated with the disease are; Rest tremor, bradykinesia, rigidity and loss of postural reflexes. The rest tremors seen in PD are usually found in the distal extremities, but they can also be seen in the lips, chin and jaw. Bradykinesia can be described as slow movement and it is a hallmark of basal ganglia disorders. Although Parkinson's patients seem to have impaired motor programes, when provided an external stimulus many of them exhibit normal movement. This phenomenon is known as kinesia paradoxica. Rigidity is often one of the first symptoms of the disease, but it is often misdiagnosed as arthritis or bursitis. Neck and trunk rigidity leads to postural deformities. Additional postural issues include, extreme neck flexion, trunk flexion and/or scoliosis. (Jankovic, 2008).

Non-motor symptoms associated with the disease include; autonomic dysfunction, cognitive abnormalities and sleep issues, among others. Autonomic dysfunction features can include, orthostatic hypotension, sweating dysfunction, sphincter dysfunction and erectile dysfunction. Neurocognitive dysfunction was tested on 537 PD patients using the Neuropsychiatric Inventory. Eighty-nine per cent of patients exhibited symptoms for at least one of the Neuropsychiatric Inventory. The results of the Neuropsychiatric Inventory were as follows: Fifty-eight percent of patients showed symptoms of depression, 54% showed apathy symptoms, 49% exhibited anxiety symptoms and 44% showed signs of hallucinations. (Jankovic, 2008).

Sleep abnormalities often seen in PD were thought to be a side effect of the medications patients were given. More recently, some physicians are beginning to view it as a part of the disease. Researchers began looking at the hypothalamic hypocretin system, a system that regulates sleep/wake cycles, to see how this system differs in Parkinson's patients. They have found that patients with PD had almost 50% fewer hypocretin neurons than the healthy control group. (Fronczek, et. al. 2007).

There are no known preventions that will stop PD, however there are some substances which have an inverse relationship with PD. Caffeine has been found to reduce one's risk for PD. MPTP, one of the toxins associated with PD was injected onto the striatum of mice. This led to an 85% decrease in dopamine levels in the area. However when the mice were given moderate amounts of caffeine, there was only a 60% decrease in dopamine levels. This study leads to the conclusion that caffeine may help mitigate some of the symptoms of PD, however this relationship is not causal. (Holden, 2001).

Nicotine, found in cigarettes, decreases the risk for developing the disease. It also inhibits the MPTP pathway, ensuring that more dopamine receptors remain intact. Additionally, nicotine has been shown to reduce the activity of Monoamine Oxidase, which causes the oxidation of dopamine. Coffee drinkers have a 30% decreased risk of developing PD, while smokers have greater than a 30% reduction risk. (Martyn, Gale, 2003).

There is no known cure for Parkinson's Disease, however, there are a full array of medications and treatments to slow progression of the disease and to relieve some of its symptoms, both motor and non-motor. Drug therapy is the mainstay of treatment. Surgical intervention, such as deep brain stimulation is recommended in severe cases. Physiotherapy, speech therapy and occupational therapy have all been shown to help Parkinson's patients as well, particularly in advanced stages of the disease. (Rajput, Rajput, 2006).

The three main drugs being given to Parkinson's patients are, Levodopa, monoamine oxidase B (MAO-B) inhibitors and dopamine agonists (DAs). MAO-B inhibitors are given to patients with mild motor symptoms, usually in the early stages of the disease. When administered in conjunction with Rasagiline, patients dropped 3-4 points on the Unified Parkinson's Disease Rating Scale. When taken with other drugs, such as SSRIs, some patients began exhibiting serotonin syndrome symptoms. Dopamine Antagonists act directly on striatal dopamine receptors and have a greater effect on motor symptoms than MAO-B inhibitors. DAs are often prescribed as a first order treatment in patients who are young at age of onset. Side effects of DAs include; nausea, headaches, sleep attacks and Impulsive Control Disorder, among others. DAs are usually supplemented with levodopa in the later stages of PD. Levodopa, also known as the gold standard in PD treatment, is the first order treatment given to elderly Parkinson's patients. Levodopa is most successful at eliminating PD motor symptoms, however, it has many side effects. (Sprenger, Poewe, 2013).

Some side effects of levodopa include nausea and dyskinesia. Being on the drug long-term causes up to ⅓ of patients to develop dyskinesias. Between doses patients can experience painful muscle spasms and the reemergence of other PD symptoms. The National Health Service of England recommends keeping the dose of levodopa as low as possible to prevent motor complications. The Movement Disorder Society recommends taking levodopa with a DA to prevent long-term motor side effects. (LeWitt, 2008).

The most common surgical intervention for Parkinson's patients is Deep Brain Stimulation (DBS). Prior to the discovery of this treatment, surgical treatment for movement disorders involved

ablations. More specifically pallidotomy, thalamotomy, and more recently, subthalamatomies. Thalamotomy relieved many of the tremors and dopa-induced dyskinesia, however it often left patients with speech and cognitive deficiencies. Unilateral pallidotomy have been shown to significantly improve contralateral tremor, rigidity, bradykinesia, and dyskinesias. Side effect of pallidotomy include, weight gain, reduction in verbal fluency, and a higher incidence of recurrent depression in patients who have a prior history of the disease. Appropriate anatomical and careful physiological screening prior to placement of the lesions may decrease incidences of cognitive or neuropsychological damage. Subthalamatomies have been experimented with as a cheaper alternative to DBS. Preliminary findings indicate that there are fewer cognitive and speech side effects than in pallidotomy and thalamotomy. However postoperative chorea occurred in more than half of patients who underwent this procedure. This remains a concern with subthalamotomy. Additional research is necessary to ascertain whether this treatment is a viable alternative to DBS. (Walter, Vitek, 2004).

Deep brain stimulation is a highly effective surgical therapy for PD and other movement disorders (fig. 1). To qualify as a

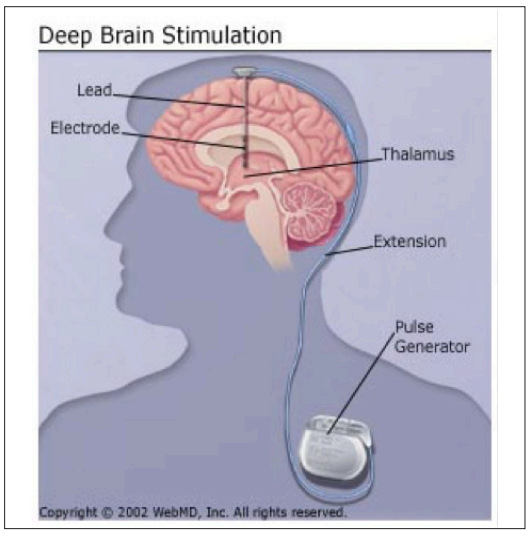

Figure 1. This drawing depicts the components of DBS

candidate for surgery, patients must be first undergo testing by a competent neuropsychologist and neurologist. A neurologist will review the patient's medical history and ensure that reasonable medical intervention has been applied. The patient will then meet with a neuropsychologist to discuss goals and expectations of the surgery. If a patient has unrealistic expectations, they are no longer an appropriate candidate for surgery. (Benabid, et. al. 2009).

Once a patient is found to be a viable candidate for surgery, they undergo basic preliminary testing. The main test involves a patient skipping a dose of levodopa at night. The patient then goes to the neurologist so he can assess the patient's symptoms without medication. Afterwards, the patient then takes his dose of levodopa, so the neurologist can see how it affects the patient's symptoms. Symptoms that do not improve with medication, usually will not improve with DBS either, hence the significance of this test (Farris, Giroux, 2011).

Once cleared for surgery the patient will undergo the procedure. The procedure involves the implantation of electrodes in the subthalamic nucleus, two lead coated wires and a neurostimulator, which is technologically similar to a pacemaker. (Farris, Giroux, 2011) Prior to the implantation of the electrodes, patients undergo stereotactic imaging to locate the subthalamic nucleus. Surgery for implantation of electrode and lead is usually done under local anesthesia, so the surgeon can determine the best location for the electrode within the subthalamic nucleus. Using microelectrodes, the surgeon will stimulate different areas to figure out where the patient will have the greatest symptomatic relief. Once the best tract is found the surgeon will replace the microelectrodes with the lead through various means. After this is done, the patient is closed up and the second part of the procedure takes place at a later date. (Benabid, et. al. 2009).

The second part of the procedure involves placing the neurostimulator in the subcutaneous pouch in the subclavicular area. This is done under general anesthesia. Once the neurostimulator is inserted and connected to the lead, the programming of the stimulator begins. Programming of the neurostimulator will usually begin a week after surgery. Voltage is increased gradually, while the patient is tested by the neurologist. Once an appropriate setting has been found for the patient, PD medication dosages are lowered to prevent dyskinesias. (Benabid, et. al. 2009).

Deep brain stimulation offers many advantages to ablations, although it is not a risk-free procedure. When performing ablations, the lesions placed on the brain are permanent and irreversible. With DBS, the neurostimulator can be turned off, or reprogrammed in case of complications. In cases of adverse effects, the neurostimulator can even be explanted. Some of the adverse effects of the implantation of the electrodes and leads in DBS include hemorrhaging, seizures and/or infection. Although these side effects are relatively rare (4%), it is important to know about them. With regard to the neurostimulator, battery depletion is an issue. Batteries have a median life of four years, but in patients with high voltage stimulation, they may last only one year. (Grill, 2005).

Studies done on the short and long term effects of the procedure on Parkinson symptoms show significant improvement in many of them. Following DBS of the subthalamic nucleus, levodopa dosages decreased on average 55.9%. Rigidity and bradykinesia symptoms decreased by 63% and 52% respectively after twelve months. Parkinsonian tremors decreased by 61% following subthalamic nucleus DBS. However, stimulation targeting the dorsal border of the subthalamic nucleus produced an 86% improvement in tremor symptoms. Gait and balance issues caused by PD are less likely to be helped by DBS. In a one year follow up study, patients were found to have the same gait and balance scores as their preoperative scores with drug treatment. (Fasano, et. Al. 2012).

One must also examine how DBS affects the non-motor symptoms of PD. As mentioned above, there are numerous non-motor symptoms which are part and parcel of the disease and DBS effects these symptoms as well in various different ways. Cognitively, DBS is safer than all other surgical interventions. The vast majority of studies indicate that patients have a decline in phonological and semantic verbal fluency tasks. This decline is noticeable shortly after surgery and may be the result of microlesions to the cortical-basal ganglia circuit, which is involved with word retrieval. An additional reason for this decline may be due to the withdrawal of dopaminergic drugs. Apathy seems to worsen following the procedure. This may be caused by the inactivation of dopaminergic receptors in the mesocortical and mesolimbic pathways after DBS. Many studies show a decrease in anxiety following DBS, this may be caused by the relief of motor symptoms. DBS seems to have little effect on autonomic symptoms of PD. Further research is necessary to better understand this. Sleep symptoms associated with PD, seemed to show improvement after DBS. This may be due to decreased bradykinesia and increased bladder capacity. (Fasano, et. Al. 2011).

Conclusion

Deep Brain Stimulation has been proven to be the most effective surgical intervention for those suffering from Parkinson's Disease. As with most medical issues, invasive surgery is not the first choice for treatment, but if necessary DBS is the gold standard in invasive treatments for PD. It provides relief to many of the motor symptoms associated with the disorder. Although success varies, it has developed into the most viable surgical treatment for PD.

List of Acronyms:

DBS	Deep brain stimulation
PD	Parkinson's Disease
MAO-B	Monoamine Oxidase B
DA	Dopamine Agonists

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