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Chana Steinberg

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Chana Steinberg will graduate with a Bachelor of Science degree in Biology in June 2022

Abstract

Parkinson's disease is a neurodegenerative disorder that currently impacts 6.1 million people globally. Although it has different presentations, its core features are tremors, postural instability, bradykinesia (slowing of movement), and psychological disabilities such as mood disorders and cognitive decline. A primary treatment is Levodopa, but it has limited success. A promising treatment called Deep Brain Stimulation (DBS) has been shown to induce significant improvements in motor skills where Levodopa has failed to help. Deep Brain Stimulation works via implanted electrodes. It has been used successfully in many studies to decrease motor issues associated with Parkinson's, but potential side effects pose a problem. Overall though, DBS is a promising field of study in the ongoing attempt to find treatments for Parkinson's disease, especially as we identify specific aspects of DBS that improve the risk to benefit ratio. This review of the current literature was conducted in order to determine the efficacy and safety of DBS as a treatment for PD.

Introduction

Parkinson's disease (PD) was first described medically by James Parkinson in 1817. Jean-Martin Charcot continued discovering more about Parkinson's disease in the mid 1800's and was instrumental in further developing the definition of Parkinson's by stating what made it a unique disorder (Goetz, 2011). Over the years, Parkinson's disease has been a subject of research, and although there is still no cure, there are many treatments aimed at relieving the symptoms. There are very effective pharmaceutical interventions available, such as the drug Levodopa. Other treatments range from traditional (lesioning of brain areas associated with PD symptoms) to new and experimental (implantation of human parthenogenetic stem cell-derived neural stem cells in animals with PD symptoms [Gonzalez, et al. 2016]). This paper will focus on discussing Parkinson Disease, and the use of deep brain stimulation to treat it. It will also seek to answer questions regarding the mechanisms, effectiveness, and drawbacks of DBS.

Methods

Available literature on the topics of Parkinson's Disease and Deep Brain Stimulation were reviewed using the search function on the Touro Library website, and by utilizing Google and Google Scholar.

Discussion

Parkinson's disease impacted 6.1 million people globally in 2016, and the rate keeps rising, as seen from the fact that only 2.5 million people had Parkinson's in 1990 (Dorsey, et al. 2018). Age is one of the most important risk factors, as more than 75% of people with Parkinson's developed it after the age of 65 (Bloem, et al. 2021), although people can develop it at a young age if they have a genetic predisposition. The main genes associated with Parkinson's disease are the SNCA, LRRK2, PRKN, PINK1, and GBA genes. Other risk factors associated with Parkinson's are head injuries and lifestyle factors, such as lack of exercise and exposure to toxins. Interestingly, smoking has been shown to be inversely related to developing Parkinson's disease, although it is unclear if the connection is correlational or causal (Bloem, et al 2021).

Parkinson's presents with many motor and non-motor symptoms. Prominent motor symptoms include bradykinesia, or slowness of movements, tremor, postural instability and rigidity. Dyskinesia, or impairment of movements, is another significant side effect that may develop with long-term treatment with Levodopa, and may cause involuntary movements that severely impact a person. There are also many non-motor symptoms associated with Parkinson's, such as dementia, depression, and dysregulation of a person's sleep cycle.

Buildup of α-synuclein in Lewy bodies and neurites is the pathological defining feature of Parkinson's disease. New studies suggest that a similar accumulation occurs in other tissues such as skin cells, which may be a helpful predictor of onset of Parkinson's as that tissue is much more accessible than brain tissue (Bloem, et al 2021). Currently PD is diagnosed clinically, based on symptoms. It may be difficult to diagnose, as the symptoms may be similar to other diseases.

Parkinson's is caused by a decrease of the neurotransmitter dopamine, which is caused by the death of cells in the substantia nigra. This is the source of dopamine production in the brain, and as cells die less dopamine is produced. Dopamine is integral in regulating movement. Loss of cells is normal with aging, but accelerated loss leads to Parkinson's; 50-60% loss indicates the onset of symptoms (Johns Hopkin's Medicine).

Replacing dopamine is not as simple as taking supplementary pills, as dopamine cannot enter the brain. Currently, a primary treatment for Parkinson's is levodopa, a drug that is converted to dopamine in the brain. However, some people don't respond to levodopa, or become resistant to it over time, or may experience fluctuations in their responses. For people who are not receiving optimal results with pharmaceutical therapies, neurosurgical treatments such as deep brain stimulation, or DBS, may be effective in controlling motor symptoms. (Bloem, et al 2021)

As explained by the Mayo Clinic, the surgical portion of DBS takes place in two parts; first, the brain is mapped out via screening tests such as an MRI, and electrodes are surgically implanted in the targeted areas. Later, in a different procedure, the battery source for the electrodes, the pulse generator, is implanted near the collarbone and connected to the electrodes via wires. In future doctor visits, the patient undergoes testing to determine the correct level of stimulation needed. Once all this is in place, ongoing supervision and tweaking of the signaling is done via a special remote control. A person may have ongoing stimulation, or it may be turned on and off via remote as needed. (Mayo Clinic, 2021).

Improvement times of symptoms vary, and are partly based on the area where the electrodes are located. For example, with subthalamic nucleus deep brain stimulation (STN DBS), tremors are relieved after seconds of DBS activation, rigidity and bradykinesia are relieved after minutes to hours, and axial symptoms may take days to be relieved. The return of symptoms once the electrode is deactivated mirrors the time of activation; for example, tremors return in minutes. This suggests that the improvements are due to different mechanisms. Quick relief of symptoms may be due to instant release of neurotransmitters, while long term relief may at least partly be due to plasticity or remodeling of the brain (Herrington, et al 2016)

DBS replaced lesioning operations, and in comparison, caused little or no tissue damage, and is therefore reversible (Groiss et al, 2009). In a postmortem case study done on the brain of a 21 year old patient who underwent DBS in the anterior thalamus for epilepsy, it was found that the DBS caused little tissue damage. The patient died unexpectedly 8 months after surgery, and an autopsy showed his death was an unexpected result of epilepsy. When studying his brain posthumously, it was found that DBD caused only mild tissue reaction and did not cause significant damage (Pilitsis, et. al. 2008)

The two primary target areas for DBS in people with PD are the subthalamic nucleus (STN) and globus pallidus interna (GPi). In a study, 299 patients were randomly assigned to either STN or GPi DBS. One hundred and fifty-two patients received GPi DBS, and 147 patients underwent STN DBS. The two groups started with similar baseline characteristics, except for minor differences in areas such as emotional well-being, social support, and cognition. Of the original group of patients, only 279 patients completed a 6-month evaluation.

At 24 months, it was found that there was no significant difference of motor symptom outcomes (based on the UPRDS III) between the two groups. There was a reduction of 11.8 in the group that received DBS-STN and a reduction of 10.7 points in the group that received STN-DBS. When the participants took the PDQ-39 (Parkinson daily questionnaire) to test quality of life, both study groups indicated improvement in 6 of the 8 subscales. Social support was slightly increased for the group with STN DBS, and decreased for GPi DBS, but no significant differences were found between the two groups. They also had similar results when testing for neurocognitive function and mood, but the group that received GPi DBS had slightly better scores on the Beck Depression Inventory, and the STN DBS group had a slight decline (P=.02).

Another finding from the study was that patients who received STN DBS were able to reduce their dopaminergic medication, as compared to patients who received GPi DBS. Additionally, STN DBS has lower amplitudes and pulse widths, which translates to lower power usage, and ultimately less frequent replacement of the pulse generator. This can contribute to lower therapy costs, and decreased risk from surgical replacement of the pulse generator (Follet, et al. 2010). This aspect is very important, as patients with Parkinson's often have a hard time with basic activities of daily living, and having to undergo surgery every couple of years is a real hardship. Anything that minimizes the amount of upkeep their hardware requires is an advantage.

In a study on the effect of STN DBS versus GPi DBS specifically on action and rest tremors in PD, 88 patients were studied in a final cohort; 57 patients underwent STN DBS, and 31 underwent GPi. They found that there was no significant difference in how the two forms of DBS treated tremors, but that STN DBS was effective more quickly. At 6 months post treatment, the patients who underwent STN DBS had more relief from tremor than the GPi DBS patients, but at the 12-month checkup the GPi group had caught up (Wong, et al. 2020).

Another study analyzed 25 patients who underwent either STN or GPi DBS. Both on and off medication, it was shown that there is not a significant difference in outcomes between the two groups. After 12 months, there was a 39 % improvement in motor scores in the GPi group, and a 48% improvement in the STN group (P<.001). Similar to results from the study above, after twelve months of DBS the STN group had a reduction in Levodopa of 38%, whereas the GPi group had a reduction of only 3%. Additionally, it was found that STN was more effective in reducing bradykinesia than GPi DBS, but GPi DBS may cause long term changes in dopaminergic systems (Anderson, et al. 2005).

Many studies have shown the positive effects of DBS on motor symptoms of PD. In a metanalysis done on 38

short term studies, STN DBS improved rigidity by 62% and bradykinesia by 52% after 12 months. GPi DBS had comparable results (Fasano, et al. 2012).

In a study done using the Deep Brain Stimulation for Parkinson's Disease Study Group on GPi DBS and STN DBS, 96 patients underwent STN DBS, and 91 underwent double blind evaluations and 6 months of follow up. It was found that there was a significant relationship between STN DBS therapeutic treatment and therapeutic effect ($p<.0001$), with treatment resulting in a 43% mean improvement in motor symptoms based on ratings from the UPDRS (Obeso, et al. 2001).

In the same study, forty-one patients received GPi DBS, 36 of whom underwent 6 months of follow up. Again, there were significant effects associated with the treatment, ($p<.0001$) with a mean improvement of motor symptoms based on the UPDRS of 32 percent. This suggests that STN DBS may be superior to GPi DBS, but both have been shown to significantly improve the motor symptoms of PD. Based on these results, it appears that DBS is an optimal therapy to treat PD, and patients who meet the criteria for it should be encouraged to explore this option. When a person experiences impaired functioning due to PD symptoms, it may be difficult to regain that functioning even if symptoms are reduced. We should be treating PD proactively, and offering treatments such as DBS as early as possible.

The previous studies discussed short term results of DBS on PD. Paul Krack et al conducted a 5 year follow up on 49 patients treated with STN DBS. When not taking medication, patients' motor symptoms improved (as rated by part III of the UPDRS) from the base line value by 66 percent after the first year, 59 percent after the third year and by 54 percent after 5 years. Additionally, before surgery 35 of the 49 patients had dystonia when not taking medication, and after a year of receiving DBS only 8 out of 43 had dystonia, and at 5 years only 14 out of 42 patients had it. However, when the patients were taking medication, there was no improvement. In fact 5 years post surgery the motor functions had decreased overall, with worsening of postural stability and freezing gait (Krack, et al. 2003). This study had no control group, but it would be interesting to see these results compared to results of patients treated only with pharmaceutical interventions.

There are a few accepted models to explain the pathophysiology of PD. One is the firing rate model. Dopamine triggers excitatory inputs to striatal direct pathway neurons projecting to the GPi, and inhibitory inputs to the indirect pathway neurons; loss of dopamine reduces both of these signals, increasing firing rates of the GPi and SNr (substantia nigra pars reticulata) neurons. Lesioning of the GPi or STN had beneficial effects on PD, backing up this theory. Alternatively, impaired functioning may due to firing patterns, or faulty oscillatory circuits, not disturbed firing rates (Chiken, Nambu, 2014). The brain is not composed of one complete oscillatory circuit; it is composed of many circuits, small and large, parallel and working together. When there is pathological oscillatory activity, especially beta band oscillations, in the circuit between the cortex, the basal ganglia, and the cerebellum, it may contribute to the motor symptoms of PD. A future area of focus therefore may be on DBS aimed specifically at disrupting these abnormal beta band oscillations, rather than general continuous DBS (Herrington, et al. 2020) When dopamine is low, as in PD, there is increased oscillatory movement in the basal ganglia. This in turn disables individual neurons, which can no longer properly process or pass on motor-related information.

Initially DBS was thought to inhibit neurons near the electrode. This theory was backed up by the fact that chemical inhibition of the STN or GPi also reduced Parkinson motor dysfunction, perhaps by release of the neurotransmitter GABA. However, currently there are many theories proposed for the exact mechanism of DBS. One that is supported by research is that DBS introduces a new electrical circuit that drowns out the faulty electrical signals in a PD patient's brain (Herrington, et al. 2020).

A study examined the impact of adaptive DBS (a form of DBS that utilizes feedback from neuronal activity to activate more selectively) on beta band bursts. The study was done on 13 patients who underwent adaptive DBS that broke up long beta bursts. The researchers found that Parkinson symptoms were relieved with short beta bursts, regardless of the frequency of the bursts, and intensified with long bursts. This effect occurs with conventional DBS as well, but with a different mechanism (Tinkhauser, et al. 2017).

Although DBS has been shown to improve motor symptoms in patients with Parkinson's disease, there is still concern regarding its effect on non-motor functions such as cognitive and psychiatric functioning. In a study, 60 patients were assigned to either SNT or GPi DBS, and 63 people were assigned to other types of treatment. The participants underwent cognitive and psychiatric assessment 6 months after the treatment. Criteria for participation were having a diagnosis of Parkinson's for at least 5 years, being below 75 years in age, having no prior or current psychiatric disorders, and being prepared to undergo neurosurgery. The participants who received DBS had bilateral stereotactic surgery, with a baseline pulse of 60 μs at 130 Hz with individualized adjustments.

The group who received alternate medical treatment received medication such as Levodopa. Cognitive tests were picked that focused on skills often affected by PD, such as cognitive skills, and had less motor skills aspects. Tests such as the Mattis dementia rating scale, the Wechsler adult intelligence test, and modified versions of the Stroop test were utilized. Participants' emotional states were measured by tests such as the Beck depression inventory and the Beck anxiety inventory. Quality of life was also assessed, with tests like the Parkinson's Disease questionnaire.

Results showed a significant improvement in motor skills and quality of life post DBS treatment, as compared to the group that received only medication. Overall cognitive functions were not impaired in participants who received DBS, but there were specific areas of decline. For example, based on the Mattis dementia rating scale, participants from both treatment plans had similar results when excluding verbal scoring, but when verbal scoring was factored in, the group who received DBS had worse results. Seven participants had reduction of more than 2 SD. By comparison, four participants from the other group had reduction of more than 2 SD. When excluding verbal fluency however, only 3 DBS participants were further away than 2 SD, as opposed to 4 participants from the other group. People from the DBS group also showed reduced performance in the Stroop tests.

The study demonstrated that people who received DBS exhibited no significant decline in cognitive or psychiatric functioning, with the possible exception of verbal fluency. They even experienced an improvement in areas such as anxiety, although that may be due to other factors such as the nature of the questions on the test (Witt, et al. 2008).

These results have also been shown in a review which analyzed studies published in England on patients with PD who underwent STN or GPi DBS. The studies included neuropsychological testing, and included at least 5 subjects who were followed for at least 3 months after their operations. The authors concluded that although different studies show different results, overall cognitive functioning decline is rare for patients that undergo DBS, and any change found is probably subtle. In addition, taking into account the significant improvements in motor function, even if DBS may be associated with decreased cognitive functions in some studies, it is still shown to improve overall quality of life (Mehanna, et al. 2017).

Another potential concern with DBS is the risk of hardware complications, or other risks associated with the surgery. In another study, 478 patients who had received DBS at a single medical center were retrospectively analyzed. Forty-one people had died. The biggest cause of death was pneumonia, with trouble swallowing being another leading cause of death. Two of the deaths were due to hemorrhaging the week following surgery. Only 22 people reported hardware troubles, including rejection, infection, and hardware failure. This study seems to indicate that hardware problems are not a significant issue in patients who undergo DBS, and other issues such as pneumonia and trouble swallowing are larger risk factors for patients with PD (Zhang, et al. 2017).

Conclusion

Parkinson's disease is a neurodegenerative disorder that impacts an increasing number of people. Although it can often be treated with medications such as Levodopa, there are times when medication alone is not effective. DBS can cause a significant improvement in motor symptoms over a long period of time. The side effects are found to be minimal. DBS is currently a very good treatment option for people struggling with PD symptoms that cannot be controlled by medication alone. As we do more research and improve DBS, it will become even more effective and safe.

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