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Deep brain stimulation in Parkinson's disease - the review

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Summary:

Introduction: Parkinson's disease (PD) is a common neurodegenerative disorder and is the second most common neurodegenerative disease after Alzheimer's disease. The clinical features are associated with motor symptoms: tremor, rigidity, and bradykinesia with postural instability. PD is also associated with many non-motor symptoms, and these often precede the motor symptoms by years or even decades. In general, treatment is based on usage of medicaments which increase a level of dopamine. Surgical therapy is reserved for more advanced cases.

Objective: To review currently available data on PubMed about a surgical treatment of Parkinson's disease and future prospects.

Abbreviated description of the state of knowledge: Surgical therapy is typically reserved for bradykinesia, rigidity and tremor in patients who no longer respond to medication in a predictable manner or who suffer medication-induced dyskinesias. Currently, the most common surgical treatment for Parkinson's disease is deep brain stimulation (DBS). Ablative procedures like radiofrequency, radiosurgery and focused ultrasound are also utilized for select tremor symptoms. We also analyzed future prospects including cells transplantation. DBS decreases a level of disability, depression and increases quality of life. It should to take under consideration in early as well as advanced PD.
Conclusions: PD is still incurable, however both pharmacological and surgical treatment can stifle the progression of disease for years and increase quality of life. New methods of treatment are promising. However, the further research about possible therapy is required.

Key words: Parkinson's disease, treatment, surgery, new therapy.

1. Introduction and purpose:

Parkinson's disease (PD) is a complex progressive neurodegenerative disease characterized by tremor, rigidity, and bradykinesia, with postural instability as the disease progresses. It was first described by James Parkinson in 1817 and further characterized by Jean-Martin Charcot. PD is the second most common neurodegenerative disease after Alzheimer's disease (AD) [1], with a prevalence of approximately 0.5–1% among those 65–69 years of age, rising to 1–3% among persons 80 years of age and older [2,3]. The median age of onset being 60 years of age [4]. Due to aging population, the morbidity of PD is going to increase.

Etiology of PD is characterized by the loss of nigrostriatal dopaminergic neurons, although neurodegeneration is not limited to only the nigral dopaminergic neurons. It is correlated with the presence of abnormal cytoplasmic deposits of protein α-synuclein within a neuronal cell body. These pathological protein aggregates are called Lewy bodies [5].

Diagnosis is based on clinical symptoms with the criteria for a diagnosis requiring the presence of two of the following clinical features: resting tremor, bradykinesia, rigidity and/or postural instability. PD is also associated with many non-motor symptoms including depression, hyposmia and constipation [6].

Currently treatment is based on replace or prevent degradation of dopamine – medicaments including levodopa, catechol-O-methyl transferase inhibitors, dopamine agonists, monoamine oxidase inhibitors. Surgical treatment is another option, especially for patient with advanced disease. Despite a decline in surgery treatment after build levodopa into treatment, surgery has become a standard adjunct to medical treatment.

The purpose of this manuscript is to elaborate currently available data on PubMed about surgical treatment of PD and future prospects of treatment.

2. State of knowledge:

2.1 Deep brain simulation

The first published surgical treatments for PD was performed in the early 1950s, and involved regions of the basal ganglia (pallidotomy and thalamotomy) [7-9]. However, the breakthrough was in 1980, when Brice and McLellan used chronic electrical stimulation of midbrain and basal ganglia to suppress tremor [10].

Deep brain stimulation (DBS) is the most common surgical procedure to amend motor symptoms of patients with advanced PD. DBS is a surgery to implant a device that sends electrical signals to areas responsible for body movement. Electrodes are placed deep in the brain and are connected to a stimulator device. Neurostimulator uses electric pulses to regulate brain activity [11]. It reduces the occurrence of "off" episodes that usually occur throughout the day in more advanced stages of medically treated PD. Electrodes can be implanted to the subthalamic nucleus (STN), globus pallidus (GP) and nucleus ventero-intermedius (VIM). However, the first and the latter are two most common targets for DBS. DBS has variable effects on other motor symptoms, such as postural and gait disturbances and non-motor symptoms including cognitive decline, sleep improvement, swallowing disturbances.

DBS can induce modifications in all components of emotion. According to Ory et al. DBS significantly reduced in the intensity of the disgust feeling among patients with PD [12]. Moreover, DBS can alter impulse control disorders (ICDs). Gee et al. Examined impact of STN DBS on ICDs. In their research, majority of patients after surgery had improvement in ICDs – the decline of hypersexual behavior, binge eating and impulsivity [13].

Urinary dysfunction is also a common problem among patients with PD. After DBS surgery symptoms of urinary dysfunctions, such as urinary frequency, urgency, and incontinence were notably relieved ($p<0.05$). The Overactive Bladder Symptom Scores and bladder storage problems were greatly improved as well ($p<0.05$). Compared with male patients, DBS surgery significantly improved the urinary symptom scores and quality of life in female PD patients *(*$P<0.05$), as well as other functional indicators related to the urinary tract, including the maximum urinary flow rate, detrusor pressure at peak flow, and residual urine volume in female PD patients ($p<0.05$) [14].

In general, DBS is adjunct treatment for patients with advanced PD. However, it can be use in early PD. Hacker et al. conducted research about impact of DBS on rest tremor progression in early PD. Unified Parkinson's Disease Rating Scale-III (UPDRS-III) was used to assess severity of disease. In compare to patients who received optimal drug therapy (ODT), rest tremor score change in UPDRS-III from baseline to 24 months was worse in patients receiving ODT vs DBS + ODT ($p = 0.002$). Moreover, more ODT patients developed new rest tremor in previously unaffected limbs than those receiving DBS + ODT ($p = 0.001$). These results suggest the possibility that DBS in early PD may slow rest tremor progression [15]. DBS in early PD may also reduce costs of treatment. Patients in the DBS+ODT group after 24 months from DBS surgery had medication costs decreased about 16% and in ODT group costs increased 72%. Moreover, DBS+ODT subjects were 80% less likely to require polypharmacy compared with ODT subjects at 24 months ($p< 0.05$) [16].

Depression and sleep deprivation are another problem which PD patients have to struggle. In other research, participants with unilateral STN DBS experienced significant improvement in depression 6 months post-operatively (4.94) compared to preoperative baseline (7.90) (p=<0.0001). Hence, unilateral STN DBS decreased a level of depression 6 months post-operatively in patients with PD. Improvement in depression is maintained over time and correlates with improvement in sleep quality and quality of life [17].
New targets for DBS are sought. Blomstedt et al. implanted DBS into caudal zona incerta (CZI). DBS group of patients with electrodes in CZI after 6 months from the operation had 41% better results in the UPDRS-III scale compared with baseline. Both groups which received and non-received drugs had unchanged scores in the UPDRS-III after 6 months. DBS in CZI had a spectacular positive effect on tremor occurrence [18]. Nucleus basalis of Meynert was another target for DBS. Unfortunately, no improvements were observed in the primary cognitive outcome [19]. New structures for DBS are constantly soughing, which may improve the efficiency of DBS.
DBS has also side effects. There are surgery risks, including misplacement of electrodes, stroke, bleeding. It can cause side effects after surgery as well. Seizure, infection, stroke headache are examples of these effects. Stimulation may cause numbness sensations, muscle tightness, speech problems, balance problems and unwanted mood changes [20].
Newer versions of the DBS components are MRI compatible, which gives the patients and their physicians more flexibility in diagnosing and treating PD as well as other conditions. More flexibility, complexity and specify of simulation due to multiple different stimulation paradigms can be programmed simultaneously. These advances allow for more complex and patient-specific programming.

2.2 Potential future treatment – cells therapy.

Currently available treatment (pharmacology and surgery) is focused on inhibition of disease progression. The efficient treatment should be aimed on causes of disease occurrence. Even though there is a wide range of knowledge about pathophysiology and changes in brain of affected patient's, PD is still uncurable.
The promising approach to treatment is cell therapy. Cell therapy for Parkinson’s disease (PD) began in 1979 with the transplantation of fetal rat dopamine-containing neurons that improved motor abnormalities in the PD rat model with good survival of grafts [21]. Canesi et al. infused mesenchymal stromal cells patients with progressive supranuclear palsy (PSP) - severe and no-option form of Parkinsonism. In all treated patients motor function rating scales remained stable for at least six-months during the one-year follow-up. It is promising result, especially when we take under consideration that PSP is severe, rapidly progressive type of Parkinsonism [22]. Lige et al. transplanted neural precursor cells as the treatment of the PD on 21 patients. In order to assess the effectiveness of the treatment UPDRS was used. Decline of symptoms, assessed by UPDRS among patients was noticed and it was statistically significant (p<0,01). No immune rejection or graft-induced side effects was observed [23].

3. Conclusions:

Parkinson's disease is the neurological disease, which affect mainly older patients. Due to population aging, PD morbidity is increasing. Currently, treatment is based on pharmacology and, especially in advanced cases surgery. Deep brain stimulation remains the main surgical option for patients. DBS is well known and constantly improving technology. It causes not only motor functions improvement (decline of tremor, bradykinesia) but also has impact on other aspects of PD. DBS alter negative emotions correlated with PD, amends functions of urinary system. Surgery stunts tremor progression in an early phase of PD and decreases need for medicaments. Decline of depression level is another one advantage of DBS.

New targets in brain stimulation which will be able to increase efficiency of DBS are sought. On the other hand, DBS is a source of wide range of side effects, correlated with operation and stimulation. Before a decision about surgery, neurosurgeon should explain profoundly advantages and disadvantages of this therapy. After that, patient can make a reasonable decision.

Cell therapy is a potential future treatment. According to data, cell therapy can mitigate symptoms of PD, without severe side effects. It gives hope that PD will become curable disease. However, further research projects are required.

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