Int J Clin Exp Med 2021;14(4):1549-1558
www.ijcem.com /ISSN:1940-5901/IJCEM0113613

Review Article

Application of deep brain stimulation in the treatment of Parkinson's disease: a review

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Received April 30, 2020; Accepted December 10, 2020; Epub April 15, 2021; Published April 30, 2021

Abstract: Parkinson disease (PD) is a chronic neurodegenerative disorder that can't be cured. It happens when brain nerve cells don't produce enough dopamine. The cause of the PD is not clear. As the disease progresses, patients may have difficulties in walking, speaking, working and even basic life. They may also have problems such as depression, sleep problems, chewing, swallowing or speech. There are no specific laboratory or imaging indicators for the diagnosis of Parkinson's disease. It is difficult to make a definite diagnosis in the early stage of the disease. Dopamine replacement therapy remained the most effective symptomatic treatment of PD. However, after dopamine treatment, there will be movement fluctuations and other side effects. In addition to drug therapy, surgery is also an effective treatment for Parkinson's disease. Deep brain stimulation (DBS) is an effective surgical method for Parkinson's disease. This article summarizes the related situation of DBS in the treatment of Parkinson disease, and prospects the development of DBS in the treatment of Parkinson disease.

Keywords: Parkinson disease, deep brain stimulation, treatment target, operative time, mechanism

Introduction

Parkinson's disease is a neurodegenerative disease characterized by loss of dopaminergic neurons in the midbrain. It is the second most common neurodegenerative disorder after Alzheimer disease. Slow movement, quiescent tremor, muscle stiffness and postural instability are the main clinical dyskinesia manifestations of PD. With the progress of the disease, psychiatric symptoms such as anxiety and depression, dementia, personality changes, as well as non-motor symptoms such as sensory disorders, olfactory disorders, and sleep disorders can occur [1]. The PD symptoms were first described two centuries ago by James Parkinson [2, 3]. It affects around 1-3% of the population over the age of 65 and its number is going to rise [4-6]. Parkinson's disease accounts for about 1.7% of the population over 65 years old in China, with an annual increase of 100,000 people [7]. Pathological changes of Parkinson's disease include degeneration and death of dopaminergic neurons in substantianigra, significant decrease of striatal dopamine content and presence of Lewis bodies in the cytoplasm of residual neurons in substantianigra [8]. The exact reason of Parkinson's disease is still unknown. Genetic factors, environmental factors, aging and oxidative stress may be involved in the process of degenerative death of PD dopaminergic neurons. Parkinson's disease may be the result of the interaction of multiple genetic and environmental factors [9, 10]. The diagnosis of Parkinson's disease mainly depends on its history, clinical symptoms and signs. There are no specific biological markers or imaging indicators for definitive diagnosis of Parkinson's disease. The main treatment methods for the PD include medication and operation. L-DOPA is still the most effective pharmacological therapy in PD [11]. In recent years, deep brain stimulation (DBS) has become a standard evidence-based therapy [12, 13].

The diagnosis of the PD

The diagnosis of Parkinson's disease mainly depends on its history, clinical symptoms and signs. Early clinical manifestations of Parkin-

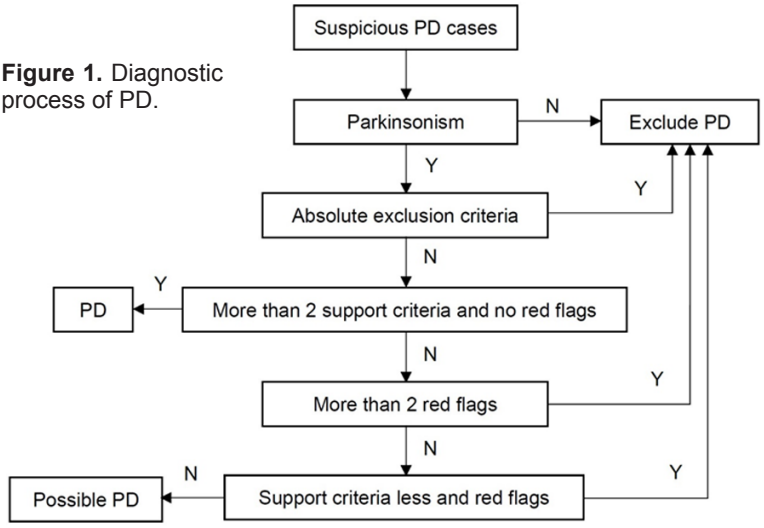

Figure 1. Diagnostic process of PD.

son's disease are atypical. It is characterized by occult onset and progressive progression. The first symptom is usually the tremor or clumsiness of one limb, which then affects the other limb. The main clinical manifestations were static tremor, motor retardation, muscular rigidity and postural gait disorder. In 2015, MDS proposed new diagnostic criteria for PD, and put forward the concepts of preclinical, prodromal and clinical stages, which are more convenient for research and clinical diagnosis. The diagnostic criteria for PD will be introduced in this paper.

The first thing for PD patients is to ensure whether the diagnosis is correct. The diagnostic criteria for PD proposed by the Movement Disorder Society (MDS) are suitable for evaluating cases [14, 15]. The diagnosis of parkinsonism is a prerequisite for the diagnosis of Parkinson disease. The diagnosis of parkinsonism is based on three core motor symptoms, bradykinesia and either a resting tremor or rigidity, which must be obvious and independent of other disturbing factors. The supportive criteria should be found to support the diagnosis of PD. The supportive criteria include 4 points. They are clear and dramatic beneficial response to dopaminergic therapy, presence of levodopa-induced dyskinesia, rest tremor of a limb and olfactory loss or metaiodobenzylguanidine scintigraphy clearly documenting cardiac sympathetic denervation. In these supportive criteria, the most important one is "clear and dramatic beneficial response to dopaminergic therapy". Because the patient is not yet on dopaminergic therapy, the result is not clear. But all patients with PD will require treatment of dopamine. The diagnosis of PD can be made till that time [16]. The next step is to make sure that the patient has no absolute exclusion criteria. The final part of criteria is "red flags", which refer to features that do not reach the level of absolute exclusion criteria [14-17]. Clinical diagnosis of Parkinson's disease requires the following conditions: (1) there is no absolute exclusion criteria; (2) there are at least two supporting criteria; (3) there are no warning signs (**Figure 1**). At present, many studies have studied the role of biological markers in the diagnosis of Parkinson's disease. Zhao et al. found that the levels of malondialdehy (MDA), 8-hydroxy-2-deoxyguanosine (8-OHdG) and DJ-1 protein were different at the different stages of the PD (**Figure 1**).

Clinical stage of Parkinson disease

In clinical practice, the classification of Parkinson's disease is still based on Hoehn-Yahr classification, but it has been revised. The revised Hoehn-Yahr has six levels (0-5). Among the six grades, two new grades, 1.5 and 2.5, have been added (**Table 1**). According to the severity of clinical symptoms, Parkinson's disease can be divided into early, middle and late stages. Grade 1-2.5 is early stage, grade 3 is middle stage and grade 4-5 is late stage. This grading can guide the follow-up treatment.

Introduction of DBS

DBS has more than 30 years' history of treating both PD and essential tremor, since first showing success as early as 1980 [18, 19]. DBS, as one of the functional neurosurgery operations, can help control the symptoms such as tremor, bradykinesia, and stiffness of PD. When medications aren't as effective as they used to be and the symptoms make everyday life a challenge, DBS may be an effective approach. Till now, more than 160,000 patients have been treated with DBS [20, 21]. DBS is a kind of

Table 1. Clinical grades of PD

Grade	Symptom
0	Asymptomatic
1	Unilateral/lateral body is affected, but not balance
1.5	The body is unilaterally affected and affects balance
2	The bilateral/lateral body is affected, but the balance is not affected
2.5	The bilateral side of the body is affected, but it can restore balance by itself under pull test
3	Balance affected, mild to moderate illness. But patients can live independently
4	Serious business activity ability. But patients can walk and stand on their own
5	Bed or wheelchair without help

treatment method which is known as neuromodulation. The effects are immediate, reversible, adaptable, and titratable without neural tissue damage. DBS consists of three parts: electrodes implanted at specific targets, connected wires and implantable pulse generator. Stereotactic method is used to precisely locate specific targets in the brain before operation. Stimulation electrodes are implanted during the operation, and send electronic signals to the target continuously, which can reversibly change the excitability of nucleus, regulate the cerebral nerve circuit, and alleviate the symptoms of patients. Although DBS has worked for many years in the clinical, many things such as mechanism, long-term outcomes, target selection, and the best operation time window are not known very clearly. The effect of DBS depends on target selection, electrode location, programming settings, appropriate medical management, age, expected benefit, and perhaps genotype, among others [22, 23]. The stimulation parameter and location could be titrated to maximize operation outcome but minimize stimulation-provoked adverse effects.

Opportunity of DBS operation

DBS is regarded as an earlier treatment option for PD. There are no strict criteria defining "earlier" use of DBS. It is usually considered that the time for the DBS is once patients are no longer benefitting from medication, or are having significant medication side effects. With the increase of relevant evidence, the concept of timing of DBS treatment is also shifting [24, 25]. In 2015, the U.S. Food and Drug Administration (FDA) gave approval for the use of DBS in PD. In this approval, the earlier use of DBS has to satisfy the following conditions: at least four years duration and with a recent onset of motor complications, or motor complications of longer-standing duration that are not adequately controlled with medication. There have been many research teams working on the optimal timing frame of DBS surgery [24-27]. Some groups investigated the potential benefit of DBS prior to the onset of motor complications [28, 29]. Christen et al. found that DBS is not considered to be a treatment of last resort (67.0%). DBS should be offered even when the disease is still manageable by medications (60.4%) [30]. Laura et al. found that the timing of DBS is dependent on disease severity and medication response. Their clinical practice evidenced the mean referral timing of less than 4 years [31, 32]. The choice of DBS treatment time should be based on the patient's condition development, medication treatment effect and patient's expectations and other aspects of comprehensive analysis.

Target selection

Appropriate target selection is the prerequisite for good results of DBS treatment. Because the mechanism of DBS surgical treatment for PD is not clear, the selection of target is mainly based on the patient's condition and the clinical experience of the operator. The most commonly used targets of DBS are the internal globuspallidus (GPi) and subthalamic nucleus (STN), while pedunculopontine nucleus (PPN), posterior subthalamic area (PSA) and ventralisintermedius (VIM) are reportedly effective targets for parkinsonian tremor control [33-37]. With the further study of PD's pathogenesis, some new targets are being explored step by step. Some RCT research indicated that the STN and GPi are equally effective in improving motor symptoms and suggested the same in

improving dyskinesia [37-40]. However, there has been discrepancy as to dyskinesia reduction between two targets. Several researches demonstrated that dyskinesia reduction from GPi was superior to STN [41, 42]. Liu et al. performed a meta-analysis to evaluate the efficacy of STN and GPi in the dyskinesia. In their research, they get the following conclusion: GPi is superior to STN in reducing dyskinesia at 12 months after surgery for advanced PD patients, and the mechanisms of dyskinesia reduction in STN and GPi are fundamentally different. STN allowed for significant dopaminergic medication reduction [43]. Neudorferet et al. found that simultaneous stimulation of VIM and STN using one trajectory is good for control of tremors [44]. Mao's meta-analysis documented that the efficacy of GPi and STN is similar in the on-medication phase and in the off-medication phase, while Vim was associated with better improvement in UPDRS scores and could be a choice for tremor-dominant Parkinsonism [45, 46]. Rughani gave some advices in their research as following: 1. If bilateral STN-DBS and bilateral GPi-DBS are equally effective in the treatment of motor symptoms of Parkinson's disease, any target of STN or GPi can be selected to improve the motor symptoms of Parkinson's disease; 2. Bilateral STN-DBS should be performed when the main objective of surgery is to reduce the dosage of dopaminergic drugs in patients with Parkinson's disease. 3. GPi should be preferred when there is no reduction in drug demand and the goal is to reduce the severity of dyskinesia caused by drugs in the "open" phase. 4. GPi-DBS or other targets should be considered if there are major concerns about cognitive impairment, especially speech speed and working memory, in patients with PD treated with DBS. 5. GPi-DBS should be considered for PD patients at risk of severe depression [47].

In a research, they found that the target cZI (Caudal zonaincerta) has shown promise in alleviating severe parkinsonian tremor. The clinical application of cZI still needs large-scale clinical data [48, 49]. With the development of genomics and epigenetics, subtypes of PD can be identified using genetic and biochemical biomarkers [50]. Future studies can use specific biomarkers to guide the selection of surgical targets for DBS and evaluate the therapeutic effect based on the expression of the biomarkers [51-54].

Postoperative management

At present, it is commonly used to turn on the machine about 4 weeks after operation. There is no literature and data against early start-up. In addition, intraoperative implantation of stimulus electrodes and therapeutic electrodes results in edema of peripheral brain tissue and instability of impedance, which is prone to side effects such as dyskinesia, dizziness and limb numbness. Some research recommend constant current stimulation mode for early programmable control [55, 56].

The complications should be avoided first after DBS operation. The common complications of DBS include hemorrhage, infection and electrode displacement. For hemorrhage and infection, the treatment programs are relatively mature. The infection range is between 0 and 15%, and the average rate is 4.5% [57, 58]. Intracerebral abscess is rare, but if it is not diagnosed in time, the result is catastrophic [59].

Programming is a very important work after operation. Accurate implantation of intraoperative electrodes is the prerequisite to achieve therapeutic effect. Intraoperative MRI-guided frameless DBS can monitor the implantation position of electrodes in real time and reduce the errors caused by brain drift after cerebrospinal fluid loss [60]. Directional controllable electrodes divide annular contacts into 3 to 4 contacts, so as to control the direction of current, form a controllable stimulation range, increase the therapeutic window. The advantages of directional controllable electrode are obvious, but its operation requirements are higher and the adjustment of programmable parameters after operation is more complicated [61]. Postoperative electrode location can be determined by imaging examination and fusion with preoperative images [62, 63]. At present, the parameters of voltage, frequency and pulse width should be set on the basis of the selection of stimulating electrode. Adjustment of parameters should be combined with medicine treatment. At present, besides the traditional program control, one way of program control also is to implement visual remote program control. The development of regula-

tion technology makes the patient's post-operative programmable control more convenient. If patients need to undergo MRI examination after operation, the magnetic field intensity requirement is 1.5T; high or low are not recommended. With the maturity of technology, the development of ultra-high field intensity MRI compatible DBS has become an inevitable trend in the future. Heat generation of DBS equipment in magnetic field is a potential risk factor affecting its safety [64, 65].

Battery exhaustion, accidental shutdown or removal of infected IPGs may rapidly worsen Parkinson's symptoms and may lead to severe DBS withdrawal syndrome [66]. Patients with early onset, longstanding and advanced disease may be more prone to these effects [66, 67]. The main determinants of IPG battery life include battery capacity, energy consumption, stimulation mode, etc. [68-70]. Low voltage stimulation, low frequency stimulation and bipolar stimulation can prolong battery life. The use of rechargeable devices can help the battery to last longer, and reduce the cost of battery replacement and the incidence of related complications [68, 71].

The development of MRI technology makes the preoperative target determination clearer and more accurate. Magnetic resonance imaging technology such as diffusion tensor imaging (DTI), susceptibility weighted imaging (SWI) and quantitative magnetic susceptibility imaging (QSM) can help operators identify nuclei more clearly and make surgical plans.

Development of related technologies

Intraoperative MRI can omit the steps of installing head frame. Robot-assisted DBS technology can not only save operation steps, but also reduce human errors and improve the accuracy of surgery to a new level [60, 72, 73]. Local field potential (LFP) is a new technology which can sum of postsynaptic potential signals recorded near the tip of the electrode. It can be divided into low-frequency oscillation, β-oscillation, Y-oscillation and high-frequency oscillation according to different frequencies. LFP can change after treatment with DBS or levodopa. LFP can be recorded by DBS electrode. DBS devices with LFP perception function can help us understand the pathogenesis of PD and the principle of DBS treatment [74-76].

Most DBS systems in current use are open-loop devices, meaning that they provide continuous stimulation that is not influenced by any input signal. Because there is no feedback regulation in traditional DBS, we can only adjust the parameters according to the clinical symptoms. Closed-loop DBS can overcome this shortcoming. It can sense the electrophysiological surrogates of PD motor signs and respond with delivery of an automatically adapted stimulation. Closed-loop DBS is still in its infancy as a long-term treatment for patients with PD [77-80]. Sensitive to the change of specific markers and stable operation are the necessary conditions for the development and popularization of this technology [81].

American scholars proposed non-invasive brain stimulation based on frequency superposition, which laid a theoretical foundation for non-invasive brain stimulation [82]. It is expected that under the guidance of MR, non-invasive brain stimulation can be achieved by using magnetic resonance guided focus ultrasound technology to intervene target tissue [83]. The clinical effect of DBS in PD is definite. With the development of technology, DBS will develop towards minimally invasive, non-invasive, miniature, intelligent and individualized treatment. Brain science related to DBS is being highly valued by all countries in the world. With the development of large data technology, it will provide a basis for the selection of therapeutic targets. Exploring the relationship between DBS and symptom improvement through biophysical computational modeling will be the direction of DBS development [84].

Acknowledgements

We would like to express our appreciation to members of Department of Neurosurgery, Taizhou People's Hospital, especially those of Functional Neurosurgery, for their helpful comments on this paper.

Disclosure of conflict of interest

None.

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