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NEUROSURGICAL TREATMENT OF PARKINSON'S DISEASE

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Resume

Parkinson's disease (PD) is a progressive incurable degenerative disorder of the central nervous system, which significantly limits the functional status of patients. Modern medicine has various methods of drug and surgical treatment of this disease. The review considers all stages of surgical treatment of PD, starting with historically interesting descriptions of resection of the precentral gyrus to stereotactic destruction by various methods of exposure and electrical stimulation of deep brain structures. Indications for each method, their advantages and disadvantages, principles of patient selection are presented. Indications for neurosurgical treatment are determined taking into account the international CAPSIT-PD criteria. Stereotactic destructions lead to irreversible changes in the brain tissue, so their widespread use is limited. Stimulation with deep electrodes has advantages in disease progression due to the ability to change stimulation parameters and the possibility of bilateral influence on motor symptoms. Surgical treatment of PD does not mean the abolition of drug therapy, but it allows to reduce the dose of antiparkinsonian drugs and their possible adverse effects. The best result can be achieved with timely surgery and correct selection of patients by a multidisciplinary medical team, taking into account the characteristics of the course of the disease, the possibility of long-term postoperative observation of the patient and correction of stimulation parameters.

Key words: Parkinson's disease; deep brain stimulation; neurostimulation; implantation of electrodes into the brain; radiosurgery for Parkinson's disease; radiofrequency ablation; thalamotomy; subthalamotomy; pallidotomy.

Introduction.

Parkinson's disease (PD) is a progressive brain disease accompanied by degeneration of dopaminergic neurons of the substantia nigra with accumulation of the protein α-synuclein and formation of Lewy bodies [1].

The most common reasons for the lack of clinical effect after SRS are insufficient volume of the necrotic focus, which can be observed even with high radiation doses reaching 120–

160 Gy [2, 3]. Focused ultrasound ablation (FUS ablation) under the control of magnetic resonance thermometry is also a non-invasive method based on the focused effect of ultrasound, which leads to local tissue heating to 43–60 °C, forming coagulation necrosis. The duration of heating is controlled by changes in the neurological status and real-time MR thermometry, which is usually 10–20 s [4, 5]. Focused ultrasound was first used by R. Meyers and the Fry brothers in the 1950s, but at that time craniotomy was mandatory for FUS ablation [6, 7]. The method was revived with the development of transcranial acoustic approaches in combination with MR thermometry, which provides less invasiveness and an accuracy of action of up to 1 mm [8, 9]. The method of thalamotomy using FUS ablation under the control of MR thermometry was approved by the US Food and Drug Administration for the treatment of essential tremor and tremor in PD [10, 11]. Data on the implementation of subthalamotomy and pallidotomy using the FUS ablation method are scarce and include the results of treating a small sample of patients with an observation period of 3–6 months [12, 13]. The effectiveness of the FUS ablation method depends on such anatomical features of the skull as the presence or absence of acoustic windows, the volume and coefficient of bone density, and the angle of application of acoustic rays to the surface [14]. L. Erin et al. described a patient with polyetiologic tremor, who developed radionecrosis 3 years after radiosurgical thalamotomy, accompanied by clinical deterioration in the form of resumption of tremor. The patient underwent repeated thalamotomy, but this time using the FUS ablation method, and 3 months later, MRI of the brain in T2 and FLAIR modes did not reveal any post-radiation changes [15]. Considering the low risk of hemorrhagic complications during FUS ablation, the reversibility of the process at the initial stages, the predictability of the size of the necrosis focus, the possibility of intraoperative clinical control, bilateral exposure to this method is actively studied. A clinical case of treatment of a patient with essential tremor is described in the literature; destruction was performed in two stages with an interval of 8 months [16]. The patient did not experience any side effects in the form of dysarthria, dysphagia, or gait disturbance. This method is of no less interest in the treatment of early stages of PD, a more detailed discussion of which will be possible only after accumulation of new data [17]. The possibility of using FUS ablation may be limited by the anatomical and physical features of the skull, as well as the rare occurrence of equipment due to its high cost. Below is a table containing the main characteristics of each destructive method of exposure in PD (Table 1). The main disadvantage of destructive operations is the irreversibility of the necrosis focus and its volume, which does not allow controlling the symptoms as PD progresses. An alternative to the destruction of nuclei can be their

stimulation with short pulses of electric current. Stimulation of the basal ganglia in Parkinson's disease Deep brain stimulation (DBS) is a chronic stimulation of deep brain structures, the parameters of which can be adjusted depending on the clinical manifestations.

The absence of irreversible brain damage, the possibility of bilateral action on symptoms, and programming of basal ganglia stimulation parameters as the disease progresses make neurostimulation the preferred option for neurosurgical intervention [18, 19]. There are several theories explaining the mechanism of action of DBS. According to the classical frequency model, DBS suppresses pathological activity of STN neurons and the medial part of the GPi. Excessive excitation of these structures due to a decrease in dopamine production leads to inhibition of thalamic neuron activity and the development of hypokinesia. The “jamming” theory states that pathological activity is modulated by DBS. Another hypothesis narrates the occurrence of abnormally synchronous pathological activity in sensorimotor circles. Recording of the local field potential from DBS STN leads at rest demonstrates an increase in the power of the field potential at β frequencies (13–35 Hz). When stimulation is turned on, the power in the β range is suppressed. Thus, by interrupting pathological oscillations, DBS helps to reduce the severity of motor symptoms. The implementation of DBS mechanisms at the cellular level is associated with the activation of astrocytes and neuronal bodies after stimulation, which is accompanied by the release of various gliotransmitters. Stimulation of VIM leads to an increase in adenosine content by converting it from adenosine triphosphate in astrocytes in the extracellular space. A study by L. Bekar et al. described a decrease in tremor severity against the background of an increase in the concentration of adenosine around the electrode in the cerebral cortex of mice. Therefore, adenosine can help increase the effectiveness of high-frequency exposure by stimulating inhibited neurons. There are other hypotheses describing a possible mechanism of action of chronic brain stimulation, but this process has not been fully studied [20, 21]. In 1967, neurostimulation was first used to treat chronic pain. For the treatment of PD, DBS STN was first performed in 1994 in Grenoble by A. Benabid et al. In 1995 in Russia, V.A. Shabalov together with V.A. Gutorko developed and implanted the first domestic neurostimulator "Neuroelectrokt" at the N.N. Burdenko Neurosurgical Research Institute [52]. For DBS, special deep electrodes are implanted in the basal ganglia, and a programmable system with a battery that delivers electrical impulses is installed subcutaneously in the subclavian region. The targets for deep brain stimulation are the same nuclei that can be subject to destruction [22,

23]. The choice of nucleus is based on the clinical symptoms of PD that dominate in the patient (Table 2). Surgery is not performed in the presence of severe cognitive impairment, affective disorders, in particular severe depression with suicidal thoughts, since an increase in mental disorders has been repeatedly described in the postoperative period, the development of which is associated with the localization of the installed stimulation electrode and the onset of chronic stimulation of the basal ganglia, changes in therapy with levodopa drugs [24]. In symptomatic parkinsonism that has arisen against the background of severe cognitive impairment, improvement in the condition after DBS is unlikely. DBS, like destructive methods, is a symptomatic treatment of PD, that is, it allows you to relieve tremor and dyskinesia, reduce the severity and severity of the "off" period, but does not allow you to completely abandon drug therapy. The following groups of complications of deep brain stimulation are distinguished. 1. Intraoperative complications (intracranial hematomas, pneumocephalus, electrode displacement). The frequency of intracranial complications is 2-3%. 2. Postoperative complications: infectious complications (skin infections, erosions at the site of implantation of the subcutaneous generator); technical complications associated with inaccurate placement of the electrode, its rupture, displacement of the neurostimulator or its malfunction. The frequency of infectious complications is from 4 to 30%. Complications associated with the side effects of stimulation: stimulation dyskinesias; axial disorders (dysarthria, postural instability, gait disturbance); sensory disorders in the form of paresthesia; movement disorders (tonic contraction of the muscles of the face or limbs); autonomic disorders in the form of a sensation of heat, increased sweating; oculomotor disorders, dizziness, anxiety attacks, euphoria, hypomanic states or apathy. These side effects usually disappear with the correction of the stimulation parameters [25]. Table 3 lists the main advantages and disadvantages of the deep brain stimulation method in PD. In Fig. 2 shows skull radiographs and CT scans of the brain with implanted depth electrodes in the STN on both sides. The intraoperative photo in Fig. 3 reflects the process of microelectrode insertion. When the subthalamic nucleus is detected, specific neuronal activity is recorded (Fig. 4). DBS in Early Parkinson's Disease Interest in DBS in early PD has been observed for many years [26, 27]. The main goals of such intervention are to prevent symptom progression and justify the risk of surgery at an early stage of the disease. In 2013 and 2018, the results of the EARLYSTIM study [28, 29] were published, which included patients with PD under 60 years of age, an average disease duration of 7.5 years, and motor fluctuations for 1.7 years. By all parameters, the results of the surgery were superior to those in the group of patients who received only conservative treatment. Data from the longest prospective

randomized, blinded pilot study demonstrate positive long-term results in the form of reduced disease symptom progression [30]. The study included 29 patients without dyskinesias and motor fluctuations, aged 50–75 years, with Hoehn-Yahr stage 2, who received specific therapy for 6 months to 4 years. They were randomized into two groups: one group underwent bilateral STN DBS and continued optimal drug therapy, while the other group received drug therapy alone. Comparing the patients' condition over 5 years, a significant improvement was found with the combined use of specific therapy and chronic STN stimulation. In the DBS group, the severity of resting tremor was lower, and the need for a combination of drugs was detected in 43%, compared with the group without DBS - 93%. The severity of dyskinesia, in its absence at the beginning of the study, by 5 years of observation was 21 and 50% in the groups with and without DBS, respectively. No statistically significant differences were found between the groups when assessing symptoms according to the UPDRS III and quality of life according to the PDQ-39 scale. Based on the results, class II evidence was assigned for reducing the risk of disease symptom progression, and approval was received from the US Food and Drug Administration for a multicenter study [31, 32]. Evidence of a reduced risk of symptom progression and the safety of long-term chronic stimulation of deep brain structures compared to standard drug therapy fundamentally change the view on approaches to the treatment of early stages of PD, expand the indications for DBS, however, in the Russian Federation there is insufficient experience with their use, and accumulation of long-term observation results is necessary [33, 34, 35]. Conclusion. The leading method of neurosurgical treatment is DBS due to the possibility of bilateral symptom correction. Destructive operations are considered with a significant prevalence of unilateral symptoms. The choice of the destruction method depends on the technical capabilities and features of a particular destruction method. At the same time, the possibility of combining various surgical technologies over time is not excluded. Among the destructive non-invasive methods in modern functional neurosurgery, preference is given to such methods as SRS and FUS ablation, radiofrequency thermocoagulation is the main method of open destructive operations, cryodestruction is practically not used. The choice of a destructive method can be limited by the availability of appropriate equipment in the patient's region of residence. Increasing attention is attracted by the results of surgical treatment of the early stages of the disease, indicating better outcomes compared to standard drug therapy. This allows expanding the indications for surgery, reducing the progression of PD symptoms, reducing the dose of levodopa, and reducing drug side effects. When choosing a method and area of impact, it is necessary to take into account the clinical manifestations

of the disease, the patient's age and level of daily activity, cognitive impairment, previous neurosurgical interventions, diseases of the central nervous system, anatomical features of the skull, the presence of concomitant diseases. Patients are selected for treatment based on the results of a multidisciplinary consultation, which includes a neurosurgeon, neurologist, psychiatrist and neuropsychologist. This approach allows for the correct determination of indications for surgical treatment and the selection of the most effective and safe treatment method for each patient. Conflict of interest. The authors declare no conflict of interest. Funding. The study was conducted without sponsorship.

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