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Surgery of Parkinson's disease: inclusion criteria and follow-up

Abstract Parkinson's disease (PD) is a progressive disturbances of movement that affects mainly the motor system. Prolonged pharmacological administration may result in insufficient control of symptoms and significant side effects. Deep brain stimulation (DBS), targeted at the STN, is a recent surgical procedure that, according to the symptoms response, allows modification of stimulation parameters; its effects are also reversible. In this paper management of surgical patients is reported. It includes patient selection, inclusion and exclusion criteria, postoperative clinical protocol. The evaluation rating scale such as UPDRS, Dyskinesias Rating Scale and Self-Reporting Questionnaire usually administrated on PD patients are analyzed. Surgical inclusion criteria are (1) idiopathic PD, (2) IV or V Hoehn-Yahr stage, (3) severe motor disability, and (4) no dementia or psychiatric abnormalities. Postoperative clinical protocol is analyzed and parameter of stimulation after surgery and at the follow up are reported. Generally DBS allows an improvement of rigidity and tremor; bradykinesia also improves with high frequency stimulation. Results obtained by continuous stimulation show a mean improvement of UPDRS of about 60% and a significant reduction in the drug intake.

Key words Parkinson's disease • Deep brain stimulation • Subthalamic nucleus

Introduction

Parkinson's disease (PD) is a progressive disturbance of movement that predominantly affects the motor system. L-Dopa-based pharmacological therapy induces a satisfactory clinical response; however, its administration for prolonged periods may result in insufficient control of symptoms and significant side effects, such as – in the majority of treated patients – fluctuations in motor response, dyskinesias, and psychiatric manifestations.

The physiopathological basis of PD includes an alteration of the loop involving both somatosensory and motor cortical areas connected, through excitatory fibers, to the putamen, which would interact with the internal globus pallidus (Gpi) via a direct or external pallidus- subthalamic nucleus-mediated inhibitory circuit. The Gpi has in its turn an inhibitory effect on the ventral lateral thalamic nucleus, which is connected to the cortex via excitatory pathways.

The subthalamic nucleus (STN) plays a crucial role in this circuit; hence, surgical removal or stimulation of the STN is a valuable alternative to medical therapy, especially in advanced disease. Advances in knowledge of the physiopathology of the basal ganglia and the evolution of neuroradiological, neurosurgical, and neurophysiological techniques have contributed to a significant improvement in the treatment of movement disorders and of PD particularly.

Surgery for PD started in the 1950s but entered clinical practice in the 1960s, with thalamo- or pallidotomy. After a period of decreased interest, new interventions for lesions of the thalamic nuclei and globus pallidus have been proposed, and, more recently, the technique of deep brain stimulation (DBS), targeted at the STN, has been introduced. Unlike the other techniques, DBS allows a reversible result and modification of intensity, frequency, and duration of stimulation, to achieve optimal clinical results.

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Patient selection

Functional neurosurgery should be performed in specialized centers where clinico-surgical expertise, technological support, and trained personnel allow the best results and minimize the risks connected with the procedures. The decision on the type of indication for neurosurgery must be based on current knowledge, through an active collaboration among the neurologist, neuropsychologist, and neurosurgeon, not forgetting the patient and his/her relatives.

The patients are evaluated by various rating scales: the Unified Parkinson Disease Rating Scale (UPDRS), Dyskinesias Rating Scale and Self-Reporting Questionnaire. UPDRS allows a quantitative motor and cognitive evaluation. It is composed of six sections, each with a score ranging from 0 (normal) to 4 (severe), and it must be administered to patients with motor fluctuations in the on and off phases. The first part includes the evaluation of the mental status, mood, behavior, and motivation. The second part includes the evaluation of normal everyday activities (activities of daily living ADL). The third part includes the motor score while the fourth is focused on therapy induced complications. The fifth and sixth parts are a modified version respectively of the Hoehn-Yahr (H-Y) staging and of the Schwab and England Scale and measure disability (a functional evaluation based on the performance of daily activities while in on and off phase).

The H-Y staging rates the severity of PD in five levels, with 1 the mildest (unilateral disturbance). Generally, patients suitable for surgery are in the 3 or 4 grades. The H-Y staging and the UPDRS display a good reciprocal correlation. The administration of these scales includes a double analysis in the morning in phase on and off and during pharmacological treatment. Preoperative evaluation also includes an accurate neuroradiological work-up (T₁-weighted and T₂-weighted magnetic resonance imaging), a detailed anamnesis, and a general clinical examination. Generally, the pharmacological therapy (levodopa, pergolide, bromocriptin, apomorphine, amantadine) is not modified in the month preceding surgery.

Inclusion and exclusion criteria

The apparently trivial but crucial aspect is a correct diagnosis of PD; the results reported in the literature show a proportion of misdiagnosis ranging from 8% to 25%. The present inclusion protocols require a disease duration of at least 5 years. This stems from the observations that the side effects of medical treatment generally require 5 years to become evident. Initial response to levodopa is considered as a prognostically favorable predictor for surgery.

Inclusion criteria for candidates for surgery are: (1) idiopathic PD, (2) IV or V Hoehn-Yahr stage, (3) severe motor

fluctuations with disabling off periods and dyskinesias during on phases, (4) no dementia or psychiatric abnormalities.

Exclusion criteria are: (1) previous brain surgery or cardiac pacemaker, (2) moderately severe parkinsonism in the context of unstable pharmacological treatment, (3) dementia as assessed by DSM criteria or severe cognitive disturbances, (4) severe psychiatric symptoms (in particular, hallucinations and depression), (5) bad general health, (6) lack of compliance at follow-up.

Surgery

DBS in PD generally involves bilateral STN stimulation. The implantation of electrodes is performed by stereotactic technique (Leksell G frame) with the patient in off phase. The procedure is performed under local anesthesia; after a burr hole, coagulation and opening of the dura, the electrode is positioned stereotactically on the target, defined by previously determined coordinates calculated according to the planes laying through the anterior and posterior commissures (-4, -4, +/-12) with respect to the intercommissural plane, intercommissural point, and intercommissural line, respectively.

During surgery macrostimulation and microstimulation can be performed, thus detecting clinical efficacy, side effects, and electrical activity of single neuronal units. During perioperative macrostimulation the intensity is modified so as to check the appearance of side effects; the stimulation is considered effective when the parkinsonian signs regress with a voltage lower than 3 V on the side opposite to the stimulation. Changes in rigidity are evaluated through changes in passive resistance to the movements of the various bodily segments, as well as during voluntary movements. Bradykinesia is assessed by measuring the amplitude and speed of the required repeated movements; tremor is evaluated both at rest and during movement.

During the surgical procedure the patients have to be evaluated by a neurologist experienced in this kind of analysis. After having localized the functional target, it is anchored to the cranial surface and connected to an external stimulator, which will be used in the following days. This phase is performed under local anesthesia.

After radiological and clinical controls, with the correct positioning of the electrodes and the lack of relevant side effects, the second intervention is performed under general anesthesia (definitive subcutaneous implantation of a pacemaker).

Postoperative clinical protocol

In the hours immediately following the positioning of subthalamic electrodes, the patient starts pharmacological

antiparkinsonian therapy (only levodopa, with standard formulations, excluding slow-release formulations). The use of dopamine agonists is avoided to allow easier clinical observation during stimulation. Normal analgesics can be used in the management of post-surgery pain.

In the case of acute psychiatric disturbances, it is advisable to use neuroleptic drugs with short latency and intermediate half-life, such as clozapine; hypnotics with short-medium duration can be used to induce sleep.

The stimulation assays generally start on day 2, with dopaminergic therapy being withdrawn for at least 8 h. The initial parameters include a continuous stimulation at 0.5 V, 60 μ s (in the case of scarce response 90 or 120 μ s) and 130–185 Hz. The parameters must be tested on all the four contacts of the electrode according to bi-, tri-, and quadripolar modality, and subsequently to the definitive implantation of the pacemaker with monopolar modality.

Follow-up is scheduled at 1, 3, 6, 12, 18, and 24 months from the implantation, then yearly. The postoperative evaluation is performed in the morning, 12 hours after drug withdrawal with four UPDRS evaluations under the following conditions: (a) in the absence of stimulation and therapy, (b) 30 min after ending the stimulation and without therapy, (c) under conditions of pharmacological "on" at least 1 h after the end of the stimulation, (d) under conditions of pharmacological "on" 30 min after resuming the stimulation. At each follow-up, daily activities and quality of life are evaluated with UPDRS ADL and Schwab and England scale under conditions (a) and (d).

The total dose of drugs is progressively reduced as much as possible (about 20% every 3 months, substituting levodopa with dopamine agonists) and stimulation is increased not more than 0.4 V at each follow-up.

Results

DBS at high frequency mainly affects rigidity and tremor, and only later bradykinesia. Generally, rigidity and tremor improve within a few minutes of continuous stimulation; bradykinesia may also improve within a few minutes, but it is more difficult to evaluate because its evaluation is dependent on the cooperation of the patient. The most-relevant clinical effect is on the "off" period, with possible marked reduction of the dose of pharmacological therapy.

The most-frequent side effects include facial spasm, contralateral hemisoma paresthesias, and abnormalities in eye movements. At high values of stimulation it is possible to observe dyskinesias.

The results obtained by continuous stimulation show a mean improvement of UPDRS of about 60% and a significant reduction in the drug intake.

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