

Acceptance date: 28/10/2024

## **PARKINSON'S DISEASE, ITS NEUROBIOLOGICAL IMPLICATIONS AND PROCEDURES NEUROCIURGICALS: A LITERATURE REVIEW**

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**Abstract:** The main aim of this article is to carry out a literature review and contribute to future research into new treatments for Parkinson's disease (PD). Therefore, through the literature review, we sought to portray the importance and understanding of the patient with PD, an individual who carries an important stigma and various complications associated with the pathology and treatment, in addition to describing and discussing advances in surgical treatment in PD, reporting updated techniques in original articles and case reports in scientific databases in the last 4 years. The original articles were selected from the following scientific databases: LILACS, Frontiers, Scielo, Nature and Medline. The pathophysiology of PD is the formation of aggregates of  $\alpha$ -synuclein ( $\alpha$ -syn), a neuronal and glial protein that aggregates to insoluble fibrils and causes the formation of Lewy bodies, which leads to the patient being affected in various areas, involving neurogenetic issues, the renin-angiotensin-aldosterone system (RAS), the enteric nervous system (ENS) and the immune system. With regard to the treatment of PD, surgical approaches are used to establish disease modifications in PD. ECP is characterized by the implantation of electrodes with direct electric current that promotes the improvement of PD symptoms, it is a technique used to control symptoms such as: tremor, dyskinesia, fluctuations, dystonia, therefore, it has become the main stereotactic technique. Among the neurosurgical and biological techniques discussed, it can be concluded that CSE was an important technique with the greatest impact, showing relief mainly of motor symptoms in patients who no longer respond to pharmacological treatment.

**Keywords:** Parkinson's Disease; Deep Brain Stimulation; Abdominal Vagotomy;

## INTRODUCTION

Parkinson's disease (PD) was originally described in 1817 by the British physician James Parkinson in "Essay on the Shaking Palsy" (RAHIMPOUR *et al.*, 2022). According to Müller *et al.* (2005), Braak carried out the anatomico-clinical correlation of PD and postulated that an unknown pathogen in the intestine or nasal cavity could initiate the loss of dopaminergic cells sporadically via the vagus nerve or olfactory tract with the occurrence of almost soluble aggregates in the neuronal body called Lewy bodies with  $\alpha$ -synuclein ( $\alpha$ -syn), ubiquitin and phosphorylated neurofilaments.

According to Santos *et al.* (2022) in Brazil, the Department of Informatics of the Unified Health System (DATASUS) showed an incidence of the condition in patients aged 60 to 89 from January 2016 to December 2020, with a higher incidence in male patients. There are several excellent reviews on medical approaches and clinical trials in PD, however, reviews on methods in neurosurgery, evolutions in neurobiology are less common, and are necessary to contribute and evolve medical treatments, and understand whether benefits can be achieved by less invasive routes. PD can still be characterized by three motor symptoms: rigidity, resting tremor and bradykinesia, as well as the occurrence of psychotic symptoms. However, PD can also show symptoms such as sleep disorders, cognitive impairment and behavioral changes, which can appear early and dominate the clinical picture during its progression, which can be explained by the relationship between the basal ganglia and the cingulate and orbital cortices, and orbitofrontal and prefrontal areas (RASIAH *et al.*, 2023).

Therefore, it can be seen that around 15% of PD patients have a family history and 5-10% have a monogenic form of the disease with Mendelian inheritance, genetic risk for the development of this pathology may be associated with the loss of functional mitochondrial

complex I (MCI) in dopaminergic neurons of the substantia nigra (GONZÁLEZ- RODRÍGUEZ *et al.*, 2021). The aim of this article is to review the literature and compare surgical treatments to alter the progression of PD.

## METHODOLOGY

This original article is a bibliographical review of several original articles, which were looked up in scientific databases such as LILACS, *Scientific Electronic Library Online* (SciELO), *National Library of Medicine* (NIH), Frontiers, Nature, PubMed and Medline. The terms used in this study referred to surgical treatment, its different approaches and finalizations. We reviewed the results and surgical methods of the existing literature and no individual patients were involved, the descriptors used in this research were: "Parkinson's disease", "cell transplantation", "administration of glia-derived neurotrophic factor, dopamine growth factors", "deep brain stimulation", "abdominal vagotomy", "radiosurgery". The data was collected between 2020 and 2024, over the last 4 years. The inclusion criteria were studies available in full and free online, articles that were case reports or literature reviews on different surgical methods, their respective technologies and the impact of their interventions, articles in Portuguese and English. The exclusion criteria for this article were the exclusion of duplicate articles, those that were not presented objectively on surgical methods, incomplete works, paid-for works and articles that were not in English or Portuguese. During the reading of these articles, the possible surgical and pharmacological interventions for the treatment of PD were discussed by the authors, and any disagreements were resolved.

A total of 39 original articles were found, of which 18 were excluded because they did not present objective results on surgical issues, and 21 were selected and studied. After

reading the title and abstract to identify the inclusion criteria, 8 original articles were selected, as shown in Table 1, to compose the review and discussion on which surgical methods have demonstrated the best results in patients with PD today. However, most of the articles found with these search terms did not demonstrate neurosurgical approaches that characterized real modification of the disease.

## RESULTS AND DISCUSSION

In Table 1, of the 8 articles, 5 presented important results about the PCE technique, in relation to the reduction in the use of drug therapy, which causes important comorbidities in PD patients, reduction of motor symptoms, already observed in various literatures, while one selected article presented the innovative surgical method of MRgFUS, One article demonstrated the use of pluripotent cells, with conclusions that their use in animals was promising, and one article discussed the method of radiosurgery in patients with PD, with clinical results, but not recommended for patients in advanced stages of the disease.

## NEUROSURGICAL TECHNIQUES AND THEIR ADVANCES IN THE CARE OF PARKINSON'S DISEASE

Individuals with PD generally use polypharmacy in their therapy and consequently have associated complications such as constipation and interactions.

This can lead to a limitation in therapeutic efficacy, or the tremor can be refractory to medication. Early in the course of the disease, medical treatment is effective in controlling motor symptoms and improving quality of life in most patients. However, with the progression of the disease and chronic use of dopaminergic therapies, patients can develop motor fluctuations and dyskinesia. Therefore, surgical and other advanced treatment options should be considered for patients whose symptoms

cannot be adequately controlled with oral medications alone (LACHENMAYER *et al.*, 2021). Despite the continuous refinement of medical and surgical therapies, the treatment of PD remains a challenge, as the therapeutic strategies adopted generally focus largely on controlling the motor symptoms of the disease, either through dopamine-based drugs or the application of deep brain stimulation (DBS) to more stably alter the function of the basal ganglia, behavioral therapy associated with neuromodulation, ablative or lesional procedures and dopaminergic drug infusion devices (TORRES *et al.*, 2024).

According to the idea previously disseminated, the surgical approaches used to establish disease modification in PD would be cell transplant therapy with stem cell-derived dopaminergic neurons to replace damaged cells, clinical trials and research into growth factors to promote the survival of existing dopaminergic neurons, deep brain stimulation of the subthalamic nucleus, abdominal vagotomy to decrease the risk of potential spread of the disease from the gut to the brain (KIRKEBY *et al.*, 2023).

According to the aforementioned author, there are a large number of pre-clinical studies in animal models on dopaminergic cell replacement therapies, in which the neurons would lead to the restoration of motor function, while avoiding the loss of efficacy and prominent side effects associated with long-term oral medications. In addition, cells grafted to the host would induce the restoration of damaged neural circuits. The first clinical attempts employed autologous adrenal autografts, but with only a brief and modest improvement in motor symptoms, however, efficacy was not demonstrated. However, the use of embryonic stem cells from blastocysts and induced pluripotent stem cells for the generation of authentic dopaminergic neurons from the midbrain were able to survive, to project axons to neurons and, consequently, to correct motor function deficits in rodent models of PD.

Article title	Author/Year	Objective	Conclusion
Subthalamic nucleus deep brain stimulation alleviates oxidative stress via mitophagy in Parkinson's disease	CHEN, Y. <i>et al.</i> , (2024)	To prove that deep brain stimulation (DBS) of the subthalamic nucleus has the potential to delay the progression of PD.	It was concluded that ECP was able to increase mitophagy, oxidative stress was reduced due to the removal of damaged mitochondria, leading to neuroprotection in PD.
Differential Cognitive Effects of Unilateral Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease	DEL BENE, V. A. <i>et al.</i> , (2024)	Investigate and compare the hemispheric effects of ECP surgery of the subthalamic nucleus in relation to ring-mode access of the nucleus subthalamic (STN).	None of the two techniques differentiated or unduly affected cognition, however, those who received STN showed a decline in verbal fluency.
Subthalamic Gamma Knife Radiosurgery in Parkinson's Disease: A Cautionary Tale	DRUMMOND, P. S. <i>et al.</i> , (2020)	To demonstrate that can be a safe option.	Clinical improvements have been achieved, and results suggest that the method should be performed cautiously in patients at risk of hyperresponsiveness.
Deep brain stimulation for Parkinson's disease	HARIZ, M.; BLOMSTEDT, P (2022)	To present how ECP can perform neuromodulation by implanting of neuropacemaker and improve the clinic of the patient.	It was concluded that PCE is still the superior and safest neurosurgical technique, showing improvements in motor fluctuations and dyskinesia.
Preclinical quality, safety, and efficacy of a human embryonic stem cell-derived product for the treatment of Parkinson's disease	KIRKEBY, A. <i>et al.</i> , (2023)	The main objective of the study was to evaluate safety, tolerability, feasibility of transplantation and surgical access intraputamenal stem cells.	It was found that the pluripotent cells used, neural progenitors, undergo terminal differentiation and become functional during in vivo transplantation. The product used facilitated clinical and surgical planning.
Subthalamic and pallidal deep brain stimulation for Parkinson's disease- meta-analysis of outcomes	LA-CHENMAYER, M. L., (2021)	Achievement of meta-analysis about the ECP studies in the internal globus pallidus and subthalamic nucleus.	It was demonstrated and concluded that ECP is directly related to increased L-Dopa responsiveness, reducing the dose by 50%, improving dyskinesia by 64%.
Comparative efficacy of surgical approaches to disease modification in Parkinson's disease	RAHIMPOUR, S. <i>et al.</i> , (2022)	Carrying out a study and comparison of data underlying the types of surgery proposed for DP	Inconclusive about surgical methods, and what would be the most suitable way to change the degree of the disease.
Effects of deep brain stimulation and verbal suggestions on pain in Parkinson's disease	ROSENKJÆR, S. <i>et al.</i> , (2024)	To see if pain is relieved through ECP, and if verbal suggestions modulate clinical responses.	It was concluded that verbal cues influence pain levels, but no changes were found in relation to the execution of PCE surgery and to pain clinic.
Correlation of visual area with tremor improvement after MRgFUS thalamotomy in Parkinson's disease	XIONG, Y. <i>et al.</i> , (2022)	To observe the effects of by magnetic resonance-guided focused ultrasound (MRgFUS) in patients with PD.	The impact is still uncertain, although the technique is new and inconclusive.

Table 1 - Sample classified according to database title of article, author and year of publication, main objective and conclusion of study

PCE is important as the treatment of choice for specific symptoms such as tremor, dyskinesia, fluctuations and dystonia, and has therefore become the main stereotactic technique for treating refractory neurological symptoms in PD patients, demonstrating an estimated 32% motor improvement in patients 10 years after diagnosis (RAHIMPOUR *et al.*, 2022). (2024) ECP consists of implanting electrodes made of thin metal material in the subthalamic region, globus pallidus or

other locations. ECP is carried out using algorithms and consequent programming of intercalation, use of fractional current and tests on each contact of the ring in a monopolar configuration with the electrode as the negative (cathode) and the implantable pulse generator (IPG) as the positive (anode), assessing the effect with clinical effect on the patient's symptoms (RAHIMPOUR *et al.*, 2022).



However, due to contraindications, other alternative techniques have been developed, such as focused ultrasound (USG) and *Gamma Knife* (GK) radiosurgery, which performs the procedure in the region of the motor thalamus, related to the improvement of bradykinesia and rigidity. Radiosurgery can be an option for patients who cannot tolerate ECP, who have contraindications or in locations where it is not permitted. In addition, radiosurgery can also cause permanent neurological complications, as around 2% of the population is hypersensitive to radiation. These patients can be treated with corticosteroids or vascular endothelial growth factor inhibitors, such as bevacizumab (DRUMMOND *et al.*, 2020).

PD involves many factors, such as gastrointestinal disturbances like delayed gastric emptying, which involves different regions of the body, thus reducing the absorption of nutrients and drugs. Other techniques include abdominal vagotomy, which could be described as preventative. According to Rahimpour *et al.*, (2022), vagotomy prevents the transfer of  $\alpha$ -syn from the colon to the CNS via the vagus nerve and brainstem. This technique can be divided into truncal and selective vagotomy, respectively disconnecting the vagus nerve from the entire intestine or its connection to the stomach. According to Beach *et al.*, (2021), patients who have undergone abdominal vagotomy show a low prevalence of developing PD, while Skjærbæk *et al.*, (2021), reported that this technique reduces the incidence of PD by 40% to 50%, with truncal vagotomy being of greater importance in this regard than selective vagotomy.

In a complementary manner, neurosurgery by focused USG guided by NMR (MRgFUS) is a new option in the treatment of patients with PD (XU *et al.*...), 2021), through MRgFUS with thalamotomy can reduce patients' refractoriness to medication, ablation of the nucleus is performed through high-intensity

energy USG without opening the skull, anesthesia or ionizing radiation, however, little is known about the impact of a focal approach on the functionality of the brain and the affected region, according to Xiong *et al.*, (2022) lesions in the tract between the thalamus and the nucleus rubro can occur with this procedure.

## **DEEP BRAIN STIMULATION (DCST) IN THE TREATMENT OF PARKINSON'S DISEASE**

The ECP method is characterized by the implantation of electrodes with a direct electric current that promotes the improvement of PD symptoms, especially dyskinesia and the reduction of drug side effects, with a clinical improvement of 30% after L-Dopa, antidromic activation of inhibitory neurons, obstruction of abnormal neuronal deflagration, induces inhibition and reduces hyperactivation of the subthalamic nuclei or internal globus pallidus, while at the same time activating the premotor cortex, primary motor cortex (ROSENKJÆR *et al.*, 2024).

PCE has become the main stereotactic technique for the treatment of neurological symptoms. This surgical method shows improvement in the patient's motor condition, although some linguistic deficits may remain. Generally, the most affected hemibody is treated with ECP, the procedure is performed under local anesthesia and the patient is awake, Midazolam 1 to 2mg is administered when stereotaxis is performed and also the use of neuronavigation for the procedure, the most suitable location for access can be verified through neuroimages already recorded by MRI and CT, which prevents *brainshift* during surgery and other associated procedures. The programmer uses a pulse width setting of 60  $\mu$ s and a frequency of 130 Hz (DEL BENE *et al.*, 2024). After the electrode has been implanted, clinical and neuroimaging tests are

carried out to verify its effectiveness, after which the parameters for electrical stimulation and definitive implantation are adjusted (CHEN *et al.*, 2024).

In addition, the electrodes are attached to the hole in the skull and connected to cables that pass through a region below the collarbone, where the cables are connected to a implantable *neuropacemaker*, this device consists of primary cells and will be replaced after its depletion usually after 5 years, or it can be rechargeable. In this way, the procedure is verified afterwards by neuroimaging, electrostimulation is applied by the neurosurgeon to the ECP a few days after surgery, via an external computer connected to the *neuropacemaker* (HARIZ; BLOMSTEDT, 2022).

## FINAL CONSIDERATIONS

PD is a neuropathology that involves several systems and has a consequent impact on the organization of the body's functions, affecting everything from the SNS to the CNS and causing significant alterations in dopamine production. Among the neurosurgical and biological techniques discussed, it can be concluded that ECP was a technique of important relevance and the one with the greatest impact, in which several studies and findings were found in the development of this article, this advanced technique presents an important minimization of the motor symptoms related to PD.

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