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The role of neurosurgery in Parkinson's disease: literature review

O papel da neurocirurgia na doença de Parkinson: revisão de literatura

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ABSTRACT: With population aging and increased life expectancy, dementias have grown significantly. The increase in the elderly population also increases the number of chronic diseases associated with aging, such as neurodegenerative diseases. Parkinson's disease is a chronic and progressive disorder of the central nervous system, specifically the nuclei of the base, involving the progressive loss of dopaminergic neurons of the substantia nigra. It is the second most common neurodegenerative disease, surpassed only by Alzheimer's disease. It is estimated that approximately five million people worldwide have Parkinson's disease and about 200 thousand individuals in Brazil. Surgical treatment in Parkinson's disease is of paramount importance for the improvement of patients quality of life. The present study aims to contribute to future research that addresses new treatments for Parkinson's disease. The aim of this article is to demonstrate, through a large literature review, the importance of surgical treatment in Parkinson's disease, addressing its indications, types and techniques, complications and impact on the quality of life of the patient submitted to the treatment in question, through bibliographical, descriptive and retrospective review of the last twenty years (1998 to 2018). Articles were selected in the databases Lilacs, SciELO, PubMed, Cochrane and Medline, in Portuguese and English languages. The terms used in the search were related to the surgical treatment of Parkinson's disease. The main surgical techniques used are deep brain stimulation with electrode implant and stereotactic ablation. It is essential that the health professionals know the surgical possibilities in Parkinson's disease, since the postoperative needs multidisciplinary follow-up.

Keywords: Parkinson disease; Parkinson disease/therapy; Parkinson disease/surgery; Neurosurgery; Deep brain stimulation.

RESUMO: Com o envelhecimento populacional e aumento da expectativa de vida, as demências aumentaram significativamente. O aumento da população idosa amplia também o número de doenças crônicas associadas ao envelhecimento, como as doenças neurodegenerativas. A doença de Parkinson é uma desordem crônica e progressiva do sistema nervoso central, especificamente dos núcleos da base, envolvendo a perda progressiva de neurônios dopaminérgicos da substância negra. É a segunda doença neurodegenerativa mais comum, ultrapassada apenas pela doença de Alzheimer. Estima-se que aproximadamente cinco milhões de pessoas no mundo possuam doença de Parkinson e cerca de 200 mil indivíduos no Brasil. O tratamento cirúrgico na doença de Parkinson é de suma importância para a melhora da qualidade de vida dos pacientes. O presente trabalho visa contribuir com futuras pesquisas que abordem novos tratamentos para a doença de Parkinson. O objetivo deste artigo é demonstrar através de ampla revisão de literatura a importância do tratamento cirúrgico na doença de Parkinson, abordando suas indicações, tipos e técnicas, complicações e impacto na qualidade de vida do paciente submetido ao tratamento em questão, através de revisão bibliográfica, descritiva e retrospectiva dos últimos vinte anos (1998 a 2018). Foram selecionados artigos nas bases de dados Lilacs, SciELO, PubMed, Cochrane e Medline, nas línguas portuguesa e inglesa. Os termos usados na busca foram relacionados ao tratamento cirúrgico da doença de Parkinson. As principais técnicas cirúrgicas utilizadas são a estimulação cerebral profunda com implante de eletrodo e a ablação estereotáxica. É fundamental que os profissionais de saúde conheçam as possibilidades cirúrgicas na doença de Parkinson, visto que o pós-operatório necessita de acompanhamento multidisciplinar.

Descritores: Doença de Parkinson; Doença de Parkinson/terapia; Doença de Parkinson/cirurgia; Neurocirurgia; Estimulação cerebral profunda.

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INTRODUCTION

With population aging and life expectancy rising, dementias have also increased significantly. The increase in the elderly population also raises the number of chronic diseases associated with aging, such as neurodegenerative diseases. Parkinson's disease (PD) was first described in 1817 by James Parkinson. In describing PD initially called it "agitating paralysis", this disease is characterized by the presence of involuntary trembling movements, decreased muscle strength, tendency to lean forward and festivity[1,2]. Between 1865 and 1880, neurologist Jean-Martin Charcot reassessed James Parkinson's work, identifying other symptoms, defining the presence of the so-called four cardinal signs of the disease: tremor, slowness of movement (bradykinesia), muscle stiffness, and balance difficulties presenting criterias for differential diagnosis and also suggesting the first treatment[3].

In Brazil, the notification of PD is not compulsory, which leads us to estimated numbers of its prevalence in the country[4]. The 2010 IBGE Census (Brazilian Institute of Geography and Statistics), points to the growth of the elderly population, in 2060, the percentage of the population aged 65 or over will reach 25.5% (58.2 million elderly), while in 2018 this proportion is 9.2% (19.2 million). The aging rate in 2018 was 43.19%, providing an estimated population of around 200,000 individuals with PD in the country. However, 10% of patients are under 50 and 5% are under 40. In addition, 36,000 new cases appear each year in the country[5].

PD affects more than 1% of the world's population over 55 and 3% over 75. It is estimated that approximately five million people worldwide have this disorder. Its incidence in Brazil is 3.3%[6]. At 70 years of age, its prevalence in the population is 550 cases per 100,000 inhabitants[7]. PD predominates in males (male-female / 3: 2), with onset between 50 and 65 years of age. The average duration of the disease is eight years (ranging from one to 30 years) and in hereditary forms, symptoms usually begin among young adults (under 45 years)[8].

PD is a chronic and progressive disorder of the central nervous system (CNS) more specifically of the basal nuclei, involving the progressive loss of dopaminergic neurons of the substantia nigra, characterized by cardinal signs of stiffness, akinesia, bradykinesia, tremor and postural instability. Its etiology is still unknown, but it is believed that genetic and environmental factors contribute to its onset. It is also stated that the aging process is closely linked to this condition due to the acceleration of the loss of dopaminergic neurons over the years[5]. It is the second most common neurodegenerative disease, surpassed only by Alzheimer's disease[6]. PD can also be secondary to other neurological diseases, such as lethargic encephalitis or Alzheimer's disease and in these cases is called Parkinson's syndrome[9]. Distinguishing PD from other disorders is important for establishing diagnosis and prognosis. There is a long list of causes of parkinsonism such as toxins, structural brain damage, metabolic disorders, and other neurological disorders, and most of them are rare. In practice, two diagnostic alternatives are considered: drug-induced parkinsonism and Parkinson-Plus syndromes (corticobasal ganglion degeneration, Lytico-Bodig dementia syndrome, multiple system atrophy syndrome, progressive palatal atrophy, and progressive supranuclear palsy). It is important to recognize drug-induced parkinsonism as it may be reversible. Dopamine antagonists, including neuroleptic agents, antiemetic drugs, and calcium channel antagonists (flunarizine and cinnarizine) may induce parkinsonism. Other drugs, such as amiodarone, valproic acid and lithium may also cause parkinsonism, but this is uncommon and the mechanisms are uncertain[8]. People who have suffered from stroke, encephalitis and trauma rule out the diagnosis of PD. The possibility of Wilson's disease, Huntington's disease, acanthocytosis and multisystem atrophy, which cause symptoms of parkinsonism, should also be excluded. In patients under 40 years and especially in patients under 21 years old who present rigidity, tremor and bradykinesia, prior to diagnosing PD, laboratory tests are recommended. These cases are called Early Parkinsonism and their treatment will differ from PD for longer duration, since they are young patients[10].

The onset of PD is usually insidious and hardly identifiable or bearer identifies the exact moment when some change occurs; usually relatives or close people who notice subtle changes. Diagnosis is essentially clinical, there is no specific test that confirm the presence of the disease and is defined in patients with progressive parkinsonism absence of unknown etiology, particularly the presentation of the extrapyramidal syndrome manifested by tremor at rest, rigidity, reflection loss posture and hypokinesia, associated with positive response after introduction of Levodopa[8,9]. There is no how to prevent, stop or cure the PD to this date[11]. Existing therapeutic approaches aim to reduce the motor symptoms of the disease in order to maintain the wearer with maximum autonomy and possible functional independence, providing a better quality of life and trying to delay the most the progression of the disease[9,11].

Currently, there are two main therapeutic approaches used: pharmacological, with much of concentrated research on improving existing drugs, and surgical as last traditional alternative. The treatment of PD patients should be early, complex and continuous. The availability of effective

pharmacological treatment has dramatically changed the prognosis of PD enabling the maintenance of mobility for many years and increasing the life expectancy of adequately treated patients[12].

In the 1950s, with the development of stereotaxis and the absence of effective PD drugs, surgical treatment gained great momentum in the United States and Europe. Despite the technological restrictions, it was at this time that the entire anatomophysiological basis of the targets used today was developed. After the development of levodopa in 1968, surgery was abandoned in most centers, only being used for special cases, especially in young patients who did not respond to drug treatment[10,13]. Levodopa, which at first seemed to be the definitive solution, over the years has turned out to have side effects as undesirable as those caused by the disease itself, such as "on-off", "wearing-off", "freezing" fluctuations and drug-induced dyskinesias[13]. Drug treatment has evolved little in recent decades and surgical methods have been used again in patients with PD, bringing quality of life to those who do not benefit only from pharmacological treatment. The surgical approach of PD aims to treat tremor, stiffness and bradykinesia, with varying degrees of success[9]. The indication for the surgical treatment of PD is due to the clinical condition of the patient, the disease's evolutionary state and its response to drug treatment[10,13]. It is necessary for the patient to be preserved in general health and to be mentally normal[10]. Currently three classes of surgery are under research, including injuries, deep brain stimulation (DBS) with lead implantation and neural transplant[9]. Surgical treatment in PD is of paramount importance for improving patients' quality of life. It is necessary to discuss possible treatments from the perspective of health professionals in order to elucidate their importance in the quality of life of parkinsonian patients and their need for an interdisciplinary approach today. This paper aims to contribute to future research on new treatments for PD. The aim of this paper is to demonstrate through extensive literature review the importance of surgical treatment in PD, addressing its indications, types and techniques, complications and impact on the quality of life of patients undergoing the treatment in question.

MATERIAL AND METHODS

This is a bibliographic, descriptive and retrospective survey of the last twenty years (1998 to 2018), related to PD and its surgical treatment, including original articles, case reports and literature reviews, as well as theses and dissertations concerning theme. To perform this work, a survey was carried out in the databases Latin American and Caribbean Health Sciences (LILACS), Scientific Electronic Library Online (SciELO), Cochrane Library and Medical Literature Analysis and Retrieval System Online (Medline), in portuguese and english languages. The time limit searched was from 1998 to 2018 (until the end of the research in May 2018). The journals were searched from December 2017 to May 2018. The terms used in the search were: Parkinson's Disease, Parkinson's Neurosurgery, Parkinson's Surgical Treatment, Deep Brain Stimulation (DBS), Stereotactic Brain Surgery and Parkinson's disease. By completing searches on each base, duplicate references were deleted. Were included texts containing general information about Parkinson's disease, such as symptoms, diagnosis and pharmacological treatment, as well as surgical treatment that is the focus of the study, and excluded texts that talk about specific aspects of the disease other than those mentioned above, such as treatment with speech therapist, physical exercise or nursing follow-up. Only freely available texts were included as reference for more careful and accurate analysis. 62 articles were selected, but only 33 were used in the review, according to the inclusion criteria mentioned above.

RESULTS

The neuropathology of PD involves the degeneration of dopaminergic neurons located in substantia nigra of the brain. It is a process by which neurons are lost in the region called pars compacta, resulting from the accumulation of proteins (mainly alpha-synuclein) in this region. According to current theories of pathophysiology, the probable mechanism of neuronal death is related to oxidative damage to cellular components, mitochondrial dysfunction, disturbed calcium homeostasis, cysteine protease stimulation, autophagy-lysosome and ubiquitin-proteasome dysfunction, and consequent alpha-synuclein accumulation in the form of aberrant tertiary structure aggregates. There is also a hypothesis that alpha-synuclein could have prionic behavior, that is, proteins with abnormal tertiary structures would have the ability to alter the three-dimensional conformation of other alpha-synuclein copies and to spread neuron to neuron[6,14]. Loss of dopaminergic terminals leads to a decrease in dopamine transporter density (DAT) that is responsible for modulating dopamine concentration in the synaptic cleft[15,16]. When symptoms are present, this reduction in DAT density can reach 90% of normal levels[15].

The pharmacological treatment of PD aims to control symptoms, not completely preventing disease progression. This is based on dopaminergic substitution, with levodopa being the most commonly used drug[15]. This drug crosses the blood-brain barrier and the CNS is converted to dopamine by the enzymatic action of dopadescarboxylase. The combination of drugs that

inhibit the action of this enzyme further favors the effects of levodopa. The efficacy of levodopa in the treatment of tremor, bradykinesia and stiffness can reach 80%. There are no absolute contraindications to treatment with levodopa and should be avoided in patients with psychotic history and special care should be taken in patients with heart disease and glaucoma[9]. Prolonged use of levodopa leads to fluctuations in motor performance as well as dyskinesia, leading to rapid changes between periods of severe akinesia and periods of mobility that may be accompanied by hyperkinesias[9,17]. Dyskinesia may appear within months of starting treatment and manifests itself through choreic or athetoid movements. Studies show that about half of patients treated with this drug, after five years, may have these complications and this proportion increases as the disease progresses[9,15]. Peripheral effects may also occur with the administration of levodopa, and translate into gastrointestinal manifestations such as nausea and vomiting and also cardiovascular, for example, postural hypotension and arrhythmias, these effects can be minimized with the use of a decarboxylase inhibitor[9]. It is generally preferable to delay initial treatment with levodopa to delay the onset of these related effects[15]. In general, in clinical practice, levodopa is almost always administered together with a peripheral action inhibitor such as carbidopa or benserazide. If levodopa is administered alone, less than 1% of the drug is likely to reach the CNS, as most levodopa will be decarboxylated by enzymes present in the intestinal mucosa and other peripheral tissues so that small amounts reach the brain circulation[12]. Dopamine agonists, amantadine, catechol-O-methyltransferase (COMT) inhibitors, and other drugs can effectively improve mobility and initially reduce dyskinesias, but usually fail after a few years[17]. There are also cases in which patients do not respond to drug treatment or develop drug intolerance, making treatment a challenge for medicine[15].

The big dilemma is which drug to start treating PD at the time of diagnosis, when the signs and symptoms are still unimpressive. Levodopa has the disadvantage of causing a number of complications as well as a questionable toxic effect. Selegiline and dopaminergic agonists have been used to good effect at the onset of the disease to try to decrease symptoms and delay the onset of levodopa use, the latter being reserved for refractory and progressive dysfunction leading to disability[8]. The prolongation of life, leading to the advancement of symptoms, the toxicity of levodopa and other antiparkinsonian drugs, the induction of dyskinesias and the greater precision and safety of neurosurgical procedures today have contributed to the increase in the number of indications for surgical treatment for PD.

Surgical treatment aims to establish a new functional balance within the base nuclei[9] and was stimulated due to the improved understanding of the functional anatomy that governs motor control and the refinement of neurosurgery, neuroradiology and neuropsychology methods and techniques[8]. It also controls adverse effects of the medication, including levodopa-induced dyskinesias. Neurosurgical treatment encompasses both ablative techniques and neurostimulation (DBS). Neurorestoration (neurotransplantation) and neuroreposition are still targets of advanced research and are not part of current therapeutic practice, but theoretically allow the restoration of degenerate neuronal units[18].

Indications of surgical treatment

The indication for surgical treatment in PD patients is based on the clinical condition of the patient and the expression of the disease in the face of drug and rehabilitation treatments. Neurosurgical treatment should be considered when drug therapy is ineffective or not tolerated or generates adversity in patients whose manifestations of PD are disabling and physical conditions including blood pressure, metabolic status and coagulation conditions are normal and mental conditions are not committed to the point of enabling them to participate in educational programs[18]. The ideal patient is one who has had a good response to medication for several years but who has developed treatment-related complications such as the on-off phenomenon and dyskinesias that cannot be clinically controlled. Patients with other forms of parkinsonism or who have significant cognitive impairment (dementia) should not undergo surgery[11]. It should also be an option in patients with unilateral symptomatology and low expressive, stable or slowly developing contralateral involvement over a prolonged period of more than five years, or when tremor is the predominant symptom, even when there is improvement with medication. Age is not a contraindication to the procedure. Systolic pressure should be maintained below 150 mmHg during the pre, trans and postoperative periods. Nonsteroidal antiinflammatory drugs, antiplatelet agents and antiplatelet agents should be discontinued for at least 10 days prior to the procedure[18].

Techniques used

In 1947 at Temple University, Philadelphia, neurologist Spiegel and neurosurgeon Wycis described a stereotactic apparatus and its use in humans to perform ablative procedures, initially called "stereencephalotomy" [19], which was based on commissures as reference points and consisted of a series of coronal brain slices, cut at constant intervals in relation to the posterior commissure on the anteroposterior axis and the midline on the laterolateral axis. These coronal slices were photographed with a millimeter reference grid arranged around the edges of each

coronal section. Using this reference grid, the surgeon could simply measure the height and laterality coordinates of the subcortical target structures identified in one of the coronal slices specified by the anterior or posterior distance of the posterior commissure. In this way, the coordinates could be easily determined just before the surgical procedures, so as to proceed with selective ablations with greater convenience. These preliminary studies have provided important insights into the localization methods needed to perform the first palidoanthstomies in the treatment of movement disorders and chronic pain in the 1950s as well as stereotactic aspirations of cystic tumors and their treatment by radioactive phosphorus instillation, initiation of intracavitary radiotherapy. The first stereotoxic procedure performed in Brazil was after the Latin American Congress of Neurosurgery in 1954, at Santa Casa do Rio de Janeiro by Paulo Niemeyer[20].

The technique of chronic stimulation of subcortical structures through permanently implanted electrodes (Deep Brain Stimulation - DBS) was proposed shortly after the introduction of human stereotactic surgery in 1947. Stereotactic ablation and DBS developed in parallel. The first use of DBS reflects stereotactic ablative surgery: both were initially performed to treat psychiatric illness. In 1987, the discovery that high-frequency deep brain stimulation was able to mimic, in a reversible and adjustable manner, the effects of ablation of functional targets revived the functional neurosurgery of movement disorders. Grenoble's group was the first to systematically study the therapeutic role of high frequency electric current in DBS and established 130 Hz as the "ideal" frequency used today in pale and subthalamic DBS[19].

Imaging systems are now integrated, from computer graphics to computed tomography, making procedures more accurate and faster[20]. Intraoperative field registration or micro-registration and evoked potentials of thalamic nuclei improved the understanding of the pathophysiology of abnormal movements and is considered the best method of physiological target localization, but should always be associated with an anatomical method. This technology is complex and costly, accessible only to a few centers. Physiological stimulation with macroelectrode is a widely used and indispensable method of functional localization worldwide. Only anatomical location, even with the most sophisticated computer programs, does not require its use[13].

From animal models of PD, the researchers developed the traditional model of the basal ganglia motor pathways, which consists of direct and indirect pathways involving the internal globus pallidus (GPi), the thalamus and the subtalamic nucleus (STN). The degeneration of the pars compacta of the substantia nigra was thought to lead to a depletion of dopaminergic output, thereby altering the balance in this cortico-basal gangliathalamocortical circuit. Further studies have shown that this traditional model may be too simplistic, since many more nuclei have been linked to the motorways of the basal ganglia. Over the years, many targets have been used to treat PD[21]. The targets for ablative surgery are the ventral and posterior pale globe, the thalamic nuclei Voa, Vop and Vim and the uncertain zone[18]. Ventro-posterior palidotomy can abolish parkinsonian tremor, stiffness and hypokinesia by reducing medial pale activity leading to decreased inhibitory activity on thalamocortical pathways. When tremor is the predominant symptom, the preferred target by most authors is still the ventral-lateral thalamus complex. Improvement of tremor by Vim and Vop lesions is attributed to interruption of the rubrotalamocortical loop by disconnecting the abnormal oscillatory circuits that potentiate the tremor[13].

Stereotactic thalamotomy is still used in an attempt to improve tremor as the most disabling manifestation of PD[8,22]. However, this procedure is being replaced by palidotomy and DBS in one of three target nuclei: thalamus, STN or GPi[8]. The significant improvement in tremor and stiffness in ventral-lateral thalamotomy contributes to better motor performance in both the on and off phase. The improvement of the on phase after postero-ventral palidotomy is slight. Generally speaking, patients have more prolonged phases, without the marked disability caused by dyskinesias before surgery. Off periods are shorter, with marked improvement in motor disability during them[13]. GPi injury or stimulation is a very effective procedure in the treatment of levodopa-induced bradykinesia, stiffness and dyskinesia. However, both procedures are effective only when patients are off, not effective when on, except for the elimination or relief of dyskinesias. Levodopa intake is also unaffected by these procedures[22]. Mainly due to its lower morbidity and neurological reversibility, stimulation is always preferred to injury[21,22,23]. On the other hand, DBS has a number of mechanical complications, a much higher incidence of infection (around 8%), high cost and the need to change the generator every four to seven years. Such deficiencies do not occur when the lesion is chosen. Another point that should be taken into consideration is the difficulty in performing DBS in third world countries due to its high cost[22]. Improvement in motor conditions in PD patients undergoing DBS implant surgery is well established in the literature[15].

In 1991, the groups of Benabid et al.[24] and Blond and Siegfried reported DBS thalamic tremor. Subsequent studies found that thalamic DBS was safer than thalamotomy and especially bilateral thalamotomy. DBS has been approved by the Food and Drug Administration (FDA) for the treatment of idiopathic PD, essential tremor and primary dystonia and obsessive compulsive disorder. DBS consists of continuous electrical pulses through one or more than four electrodes on a chronically implanted

electrode. The DBS electrode is placed in the target neural circuit using stereotactic functional neurosurgery and electrophysiological mapping. The electrode is connected to the internal pulse generator, which is placed in the subclavicular region. The whole system is internalized[23]. DBS alters neural circuit activity and neurotransmitter activity, exerting an effect similar to blocking spontaneous target structure activity within and beyond the stimulation field[18,23]. The cellular mechanisms of neurostimulation are unknown. Theoretically low-frequency stimulation activates neurons and axons that are close to the electrodes and inactive when the stimulation frequency is high[18]. The choice of activated electrodes and pulse amplitude (voltage) will change the location, volume and shape of the electric field. Other adjustable parameters include pulse width and DBS frequency. Low pulse widths (PW, 60s) mainly affect myelinated axons, while longer PWs may also affect the sum of cells[23].

Once the pacing target has been chosen for the patient, the general surgical procedure for implantation of the DBS unit follows similar basic steps, imaging guided target localization, physiological confirmation of the target using MERs and macrostimulation, and implantation of the final DBS terminal and ligation to a programmable internal pulse generator. Traditionally, image-guided targeting begins with the identification of consistent reference points, the anterior and posterior commissures (CA and CP), which form the basis of the Talairach coordinate system. Then the target of choice is located by measuring known distances from AC and PC. Unfortunately, this indirect method does not take into account individual anatomical variability. Magnetic resonance imaging (MRI) offers better resolution to allow direct visualization of some nuclear boundaries, which may help explain some individual variations, however, MRI may have problems with spatial distortion. The use of contrast-enhanced MRI for preoperative trajectory planning may help to avoid grooves and vessels, which reduces the incidence of bleeding complications. Recently, there have been reports of better anatomical guidance using the red nucleus as a reference. Given the limitations of current imaging-guided targeting methods, intraoperative physiological confirmation plays a critical role in the implementation of DBS. Translating target coordinates from the image space to the patient's physical space is traditionally performed using a rigid frame, such as the Leksell or Cosman - Roberts - Wells (CRW) frame. More recently, there have been developments of rapid prototyping miniframes and frameless stereotactic systems, with supposedly equivalent or better accuracy than traditional frames, as well as improved patient comfort. Intraoperative physiological localization is usually performed under local anesthesia, however patients with severe dystonia or pediatric patients may require general anesthesia. Tungsten or platinum-iridium microelectrodes are used to record single-unit extracellular action potentials. MER can detect transitions between gray and white matter based on waveform differences and different nuclei based on characteristic feeding patterns. Identification of kinesthetic neurons, whose trigger frequencies are modulated by motion, can help locate motor areas. More refined somatotopic mapping within a particular motor area can be achieved by motion-related cells corresponding to movements of specific parts of the body. Macrostimulation usually provides final confirmation of the optimal target site and is performed on the patient awake at clinically relevant stimulation parameters. When the final position of the DBS electrode is determined, it is important to confirm that the threshold for clinical benefit is substantially lower than the threshold for expected adverse effects. After determining the desired physiological target, the quadripolar DBS electrode is inserted[21].

Side effects induced by pacing can be eliminated by turning off pacing or changing active contact or other pacing parameters. Universal complications to any target include intracranial hemorrhage, lead migration, skin erosion, and lead infection. Cases of superficial infections can be treated without hardware removal[21]. The disadvantages of neurostimulation are the need for frequent patient attendance at the care unit for regulation of stimulation parameters, the occurrence of infections that require removal of the system and treatment with antibiotics, erosion of the integument covering the equipment, displacement of the electrode, electrode break or connections, battery depletion and generator defect[18].

Prospective, randomized, controlled studies show that DBS is the standard of treatment for appropriately chosen PD patients. Target selection should be based on the symptoms to be treated[21]. Neither DBS nor dopaminergic medication can prevent or treat late signs of PD, such as cognitive or axial motor deficiencies (postural stability, swallowing, speech, and gait freezing). Therefore, it can be useful to refer good candidates to DBS before they are disabled and before they have been diagnosed with dementia. In countries where DBS is not available, unilateral ablations in the thalamus, GPi and STN have been used successfully in the treatment of PD, tremor and dystonia, although the therapeutic effect may not last longer than the DBS. Bilateral injuries are avoided due to the high risk of worsening speech and balance[23]. DBS is an expensive procedure, and economic health issues should be considered. However, the amount of drug therapy needed in operated patients was about a third less than the amount required by those undergoing drug treatment. Thus, the cost of surgery should be partially offset by the reduction in the amount of drug therapy required by operated patients[25].

DBS has been shown to be effective in people

with PD refractory to clinical treatment in prospective controlled studies on both motor function and quality of life. However, it is not clear what the effects of DBS are on non-motor aspects of PD. DBS has led to improvements in function and quality of life for many people who suffer from movement disorders[24].

Studies evaluating the effectiveness of surgery in PD are based on comparisons of motor scores before and after surgery, especially according to the Unified Parkinson's Disease Rating Scale (item III) motor function scale. Other scales, such as Hoehn and Yahr, Schwab and England, have also been used. Many studies have been conducted mainly evaluating the motor aspect, comparing the pre and postoperative scores. It can also be evaluated with the UPDRS scale (item - II) the activities of daily living[26].

Stereotactic procedures in molecular neurosurgery provide suitable methods for introducing genetic material into brain tissue. Microcatheters may be stereotactic implanted toward specific structures. Some techniques of stereotactic and functional neurosurgery, born in the last century, come to integrate with molecular biology and together with gene therapy become multidisciplinary. From a purely ablative surgical discipline, neurosurgery also becomes restorative, committing itself to cell therapy techniques[27]. The use of homologous embryonic cells, cultured heterologous cells from animals, amytotic cells from neurotransmitter-producing tumors and neurohumores, autologous and cultured stem cells treated with genetic engineering techniques, are promising possibilities in the treatment of degenerative neuropathies, including PD. However, many issues still need to be resolved for neural implants to be assimilated in the treatment of PD disease, including the role of transplantation in functional recovery, the mechanisms by which neurons incorporated into the brain of the host contribute to functional improvement, such as factors Trophic factors promote functional improvement, which trophic factors are involved, what are the best source of cells for the procedure, and whether cells that induce regeneration are different from those involved in the degenerative process. Most studies used various neural or paraneural tissues for transplants. Both dopaminergic and paraneural tissue grafts of the adrenal medulla have not yet proven effective in treating PD. The functional improvement observed with mesencephalic fetal tissue implantation is more consistent and longer than with the adrenal medulla tissue implantation. Embryonic mesencephalic tissue is more viable and after implantation, its efficacy is better. There is doubt whether embryonic tissue may be a good source of dopamine or neurotrophic factors. Unresolved biological and ethical issues limit their use in clinical practice. Cell lines developed to release specific neurotransmitters or growth factors have several advantages over other donor sources. Cells modified to produce nerve growth factor have been shown to be able to prevent the death of basal telencephalon cholinergic neurons that degenerate after fornix transection. Modified fibroblasts to produce dopamine attenuate motor impairment in parkinsonian rat models. However, several studies demonstrate the difficulty of genetically transforming cells to produce dopamine, since genes for many enzymes along catecholamine biosynthesis need to be inserted for dopamine production. The risks of these treated heterologous tissue procedures include oncogenesis, viral and prion infections. There is also concern about the duration of gene expression. It is likely that in the near future, autologous stem cells will be implanted in the brain parenchyma to supply neurotransmitters and trophic factors for degenerating neurons[18].

DISCUSSION

According to the studies analyzed, thalamotomies were effective for patients with tremor, stiffness and, to a lesser extent, drug-induced dyskinesias, while palidotomies were more effective for stiffness, bradykinesia and dyskinesias. For the most severe patients, for greater benefit, combined procedures should be performed (thalidotomy associated with palidotomy or bilateral palidotomy). Bilateral injuries, mainly thalamotomies, are prevented by the relatively high rate of speech problems. Bilateral palidotomies or thalamotomy and palidotomy in the same hemisphere, or contralateral, are lesions with a low rate of serious complications. Severe patients with intense bradykinesia benefit less from amelioration of symptoms on one side of the body. Although the treated body side may be relatively or completely controlled, the inability of the other dimide impairs overall motor performance[13]. Aguiar et al.[28] concluded that one year after VIM-thalamotomy or PPV, most patients had prolonged motor benefits from the off period and control of dyskinesias in the on period, with minimal persistent complications[28]. For Samuel et al.[29], The most significant effect after unilateral ventral medial palidotomy in PD is decreased contralateral dyskinesias, while ipsilateral and axial dyskinesias improved to a lesser extent. The presence of disabling dyskinesias, therefore, remains the main current clinical indication for palidotomy. Improvement in underlying parkinsonism is less pronounced, but correlates significantly with ventrality of the medial palidotomy. However, palidotomy is associated with a significant risk of morbidity and mortality, and potential adverse events should be weighed against expected improvements in dyskinesias and bradykinesia scores. Postoperatively, resolution of levodopa-induced dyskinesias may allow some patients to tolerate higher

doses of dopaminergic medication in order to further improve underlying parkinsonism[29]. NTS injury is a very effective and safe operation, with low recurrence rate and acceptable complication incidence. The most feared complication, dyskinesia, can be successfully treated in the same surgical procedure or later by injury to another target, Vim / VOp or GPi, without increasing the incidence of complications[22]. Subtalamic neurostimulation resulted in a clinically significant improvement in the quality of life of patients under 75 years of age who had advanced PD with severe fluctuations in mobility and dyskinesia[17]. STN or GPi DBS has been shown to carry marked motor benefit in patients with advanced PD. Rodriguez-Oroz et al.[30] found that four years after STN or GPi DBS surgery, motor severity and disability are less reported than at baseline, despite the progressive and severe nature of the underlying disease process. The degree of motor improvement was the same at one and four years postoperatively, indicating a sustained beneficial effect on patients, despite maintaining a 50% reduction in daily levodopa dose from baseline. This sparing effect of levodopa was not found in patients treated with pale stimulation[30]. Neurostimulation leads to improvements in function and quality of life for many people with movement disorders[24,31]. Limousin et al.[32] concluded that chronic thalamic stimulation is effective in treating PD tremor and identified a slight but significant improvement in the stiffness and akinesia of these patients. UPDRS functional score significantly improved[32]. For Weaver et al.[33], DBS was more effective than the best medical therapy to alleviate disability in patients with moderate to severe PD with levodopa-responsive motor complications and no significant cognitive impairment. The extent of benefit was similar for younger and older patients, although adverse events were greater in older patients. Patients receiving DBS gained a mean of 4.6 hours per day of on time without troubling dyskinesia and off time decreased by 2.4 hours per day[33]. The better motor functioning experienced by patients receiving DBS was accompanied by significant improvements in quality of life[17,33]. According to Schuepbach et al.[31] neurostimulation was superior to drug therapy only at a relatively early stage of PD, before the onset of severe disabling motor complications, and may be a therapeutic option for patients at an earlier stage than current recommendations suggest. Neurostimulation in combination with medical therapy may therefore improve motor symptoms better than medical therapy alone at this early stage[31].

FINAL CONSIDERATIONS

Stereotactic surgery for PD is a procedure that can improve patients' independence in daily tasks, especially in the first six months after the procedure, without being associated with severe and lasting complications. Surgery contributes to the improvement of fluctuations, decreasing the periods and severity in the off phase, increasing the on phase, reducing dyskinesias, leading to an improvement in the performance and performance of daily activities and, therefore, benefit in the quality of life of these patients.

It is essential that health professionals know the surgical possibilities in PD, since the postoperative needs multidisciplinary follow-up. There is a need for training of specialized doctors, nurses and multidisciplinary staff to deal with patients with these complex disorders and devices. Physical therapy and speech therapy can help the patient with moderately severe parkinsonism. In advanced cases, quality of life can be improved by certain measures, such as placing extra rails or bars at home, longer-handled table cutlery, non-slip table protectors and voice amplifiers.

Further research is needed to identify the best criteria for selecting surgical candidates and choosing optimal targets for future neuromodulation therapies. Patients should be encouraged to learn about their illness (reading educational material provided by the organizations dealing with it) and to stay active physically and socially.

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