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PATHOPHYSIOLOGY AND DIAGNOSTIC STRATEGIES FOR PARKINSON'S DISEASE: A LITERATURE REVIEW

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Abstract: INTRODUCTION: Parkinson's disease (PD) is associated with a progressive neurodegenerative disorder that compromises dopaminergic neurons. The disease mainly affects the elderly, but can also occur before the age of 50. However, there is still no diagnostic method to guarantee an early diagnosis, which makes the disease's prognosis difficult. The aim of this study is therefore to describe Parkinson's disease and the possibilities for diagnosing it. **METHODS:** For this purpose, bibliographic research was carried out in the Google Scholar, *Pubmed*, *SciELO*, and Virtual Health Library (VHL) databases, with articles dated 2016-2024, in English and Portuguese, using the following keywords: "*Biomarkers*", "*Clinical Diagnosis*", "*Neuroimaging*", "*Pathophysiology*", "*Parkinson's Disease*". **RESULTS:** The diagnostic methods used for PD consist of criteria and scales that assess the individual's motor functions at a clinical level. However, through neuroimaging techniques, it is possible to perceive a greater correlation of how the regions affected by the disease behave, managing to capture structural and functional components that help to understand the progression of Parkinson's disease. In addition, it is possible to see the prevalence of genes and proteins that function as biomarkers present in body fluids (blood, CSF and saliva), which suggest changes in the disease due to their high sensitivity and specificity during the course of PD. **Conclusion:** Therefore, the evolution of research suggests that correlating clinical diagnosis, neuroimaging and biomarkers, brings great possibilities in the discovery of patients with PD, enabling the best therapeutic choices that can offer a better quality of life to individuals affected by this disease.

Keywords: Diagnosis. Neurological disease. Pathophysiology.

INTRODUCTION

Parkinson's Disease (PD) is a degenerative pathology in which there are prodromal symptoms - rapid eyeball movement during sleep, constipation and hyposmia - impaired motor function and also the development of psychological or cognitive disorders such as anxiety and depression (Armstrong; Okun, 2020). These conditions result from the death of neurons responsible for communication, mainly in the nigral and extra-nigral dopaminergic pathways (Surmeier; Obeso; Halliday, 2017).

In this sense, dopamine is an important hormone that acts as a neurotransmitter (NT) (Latif *et al*., 2021), which is part of the catecholamine family. Dopamine's role in the human body is associated with motor and cognitive functions (Armstrong; Okun, 2020), so when its levels are reduced due to the cell death of neurons, it can contribute to the reduction of the substantia nigra, located in the midbrain (Opara *et al*., 2017). According to Dorsey and Bloem (2018), neurological disorders are the main factors that contribute to the disability of individuals worldwide, and given the high prevalence of PD, which surpasses even the growth of Alzheimer's, it is clear that by the year 2040 between 12.9 and 14.2 million people will be affected by PD. However, the same authors report that due to underreporting, the figures may be higher than this (Dorsey; Bloem, 2018).

With improved health conditions and increased longevity, the rise in PD cases may be associated with these factors (Stuttrup; Warnecke, 2016; Araújo *et al*., 2024). The first symptoms of the disease appear from the age of 50, but have a higher prevalence in individuals over 80 years of age, and in males (Suttrup; Warnecke, 2016; Tolosa *et al*., 2021). Patients under the age of 50 may be affected, but this is a rare form of the disease (Khan *et al*., 2018). In addition, the age-standardized prevalence of YOPD (*Young Onset Parkinson's Disease*) has been found to be 10.2 per 100,000 people globally (Nabizadeh, 2024).

In view of this, the identification of biomarkers to improve the detection and early diagnosis of PD (prior to apparent neurodegeneration) is of paramount importance so that the patient can make better use of the therapy and have a better quality of life during treatment (Polissidis *et al*. 2020). In addition, there are other diagnostic techniques of great relevance, but which present some obstacles to their complete efficiency. In the meantime, this research aims to describe the pathophysiological processes of PD, as well as the strategies used for clinical diagnosis, neuroimaging, and diagnostics based on molecular biology.

MATERIALS AND METHODS

To compose the theoretical basis, bibliographic research was carried out in the Google Scholar, Pubmed, *Scientific Electronic Library Online* (SciELO) and Virtual Health Library (VHL) databases. Based on the inclusion factors, articles suitable for reading were selected according to the criteria of diagnosis, techniques, samples used in the tests, pathophysiology, as well as the historical context, dated from 2016 onwards.

However, the exclusion factors were those related to the care of patients suffering from PD, articles that addressed the genes of neurological diseases but did not mention Parkinson's, and those that preceded 2016. Thus, a total of 76 articles were selected, which are arranged in this paper in English and Portuguese, from 2016 to 2024, of which, when searched, the following keywords were used: "*Biomarkers*", "*Clinical Diagnosis*", "*Neuroimaging*", "*Pathophysiology*", "*Parkinson's Disease*".

RESULTS AND DISCUSSION

PATHOPHYSIOLOGY

The pathophysiology of PD is currently considered one of the most complex, since there are several causes that culminate in the development of the established signs and symptoms (Santos *et al*., 2022). Thus, there are neurological manifestations that direct the course of the disease, represented for example by the possible causes resulting from the degeneration of dopaminergic neurons (Ransohoff, 2016).

PD was first described in 1817 by the physician James Parkinson, who published a monograph based on five chapters entitled "*An Essay on the Sharing Palsy*", in which he established the characteristics of the disease, such as the observation of involuntary tremors, reduced muscle strength, tendency to tilt the trunk forward, and the "passing" from a gait to running, without impairment of the senses and intellect, as well as the prevalence of pathognomonic symptoms, associated with a theoretical reference, under a study focused on his patients who presented a peculiar symptomatology (Teive; Munhoz; Lees, 2017).

However, the term and the symptoms determined by Parkinson's generated contradictions on the part of scholars trying to understand how the meaning of paralysis was not related to other disorders, such as a disorder in the spinal cord. Thus, it wasn't until the 19th century that the neurologist Charcot attributed the prevalence of tremors to James Parkinson's disease (Berrios, 2016).

James was able to determine PD for the first time through motor signs and symptoms, which to this day are commonly used to clinically diagnose the disease. However, it is now known that there are non-motor symptoms. Thus, PD symptoms can be divided into two strands: motor and non-motor symptoms (Azevedo, 2018).

The occurrence of motor symptoms is related to the pathophysiology of the decrease in dopaminergic neurons, which consequently contributes to the reduction of the substantia nigra (Azevedo, 2018). In this context, PD patients often have bradykinesia (i.e. slower voluntary movements), muscle rigidity, resting tremor in the jaw, lower limbs and with greater predominance in the upper limbs, as well as loss of postural reflexes (Magalhães *et al*., 2022).

Regarding non-motor symptoms, constipation, depression, sleep disorders, hyposmia (low olfactory sensitivity) can be highlighted, in addition, with the progressive course of the pathology, signs and symptoms related to the impairment of other systems are perceived, such as urinary disorders, autonomic dysfunctions, pain, hallucinations and dementia (Albuquerque, 2017).

Thus, in order to transpose such studies, some authors such as Varmes *et al.* (2024) have reported that the presence of non-motor symptoms can begin even before the onset of motor symptoms in patients with a predisposition to PD, and it has been found that when these symptoms are verified in advance, they can contribute to the effectiveness of the diagnosis, as well as understanding the progression of the disease. In addition, the disease may be associated with a generalized condition of motor syndromes of multifactorial origin, but without the death of dopaminergic neurons, called Parkinsonism, presenting symptoms similar to PD (Campêlo, 2017).

PARKINSONISM

According to Zhang *et al.* (2018) the condition of Parkinsonism or Parkinsonian Syndrome, corresponds to a set of motor disorders under which Parkinsonism can be confused. Thus, according to Melo *et al.* (2023), the classification of parkinsonism can be defined as primary or secondary, depending on the risk

factors it is linked to. Thus, primary parkinsonism consists of a genetic predisposition or idiopathic causes; secondary parkinsonism, on the other hand, can be determined by drug use, exposure to toxins, trauma, vascular dementia and infections such as HIV (*Human Immunodeficiency Virus*) or Syphilis, the latter of which is an aggravating factor as it can trigger the condition of Neurosyphilis (Lima *et al.*, 2022).

In line with the genetic inheritance pointed out by Aguilera *et al.* (2020), some epidemiological data can be confirmed, which indicate that when first-degree family members are affected, there is a high prevalence (about two to three times more) of the risk that subsequent generations have of developing the disease. In addition, the inclusion of environmental factors, such as smoking, alcohol consumption and exposure to urate, are considered determinants for the development of the disease and are closely related to secondary Parkinsonism (Tysnes; Storstein, 2017).

In addition to these two classifications, it can be seen that studies have contributed to the understanding that the classification of parkinsonism plus is incorporated, establishing a condition under which degenerative diseases of an akinetic-rigid nature are included (i.e. muscle rigidity associated with slowness in the execution of movements) with symptoms that are generally not present in PD (Silva, 2017).

THEORIES OF DOPAMINERGIC DEGRADATION

The neuroanatomy of some regions of the brain of rodents and primates is made up of the set of cell bodies of neurons located in the subcortical portions, which are important in interneuronal communication. These regions are known as the Basal Nuclei and are made up of structures called: the caudate nucleus, the lentiform nucleus (subdivided into the putamen and internal and external globus pallidus portions), the subthalamic nucleus and the substantia nigra, which can be divided into pars compacta and pars reticularis (Gerfen; Bolam, 2017).

In addition to these nuclei, PD mainly involves the caudate and putamen nuclei - which form the striatum - as well as the substantia nigra pars compacta. These structures comprise the nigrostriatal dopaminergic pathway, from which cell bodies of the midbrain extend via axons, bifurcating into the striatum and forming various projections of dopaminergic neurons (Hou *et al.*, 2017).

In this sense, impairments in the respective areas can result in deleterious effects that debilitate the individual's life, since these regions are associated with cognitive, motor and behavioral aspects (Howard *et al.*, 2018). Thus, the destruction of these neurons in PD causes a decrease in the tone of the substantia nigra pars compacta, due to the degradation of neuromelanin contained in dopaminergic neurons (De Sousa Costa *et al.*, 2023). In turn, there is dopaminergic denervation, mainly along the nigrostriatal pathway. This allows up to 80% of dopaminergic neurons to be destroyed in the striatum, causing the motor signs and symptoms associated with PD (Pagano; Niccolini; Politis, 2016).

In addition to these neuroanatomical regions, according to Barber *et al.* (2017), dopaminergic loss must begin in other portions, such as the lower brainstem and antecedent olfactory structures. Thus, studies by Poewe *et al.* (2017) and Michel, Hirsch and Hunot (2016) point out that there are several theories that result in the possible causes of this destruction of dopaminergic neurons, which can be highlighted mainly: protein aggregation and neuroinflammation.

Protein aggregation

The process of protein aggregation is evidenced by a protein called alpha-synuclein that favors the increase of structures called Lewy bodies, capable of altering the gray matter (Azevedo, 2018).

Thus, alpha-synuclein is commonly found in the cytoplasm of neurons - being soluble - more specifically associated with presynaptic terminal membranes because it is responsible for the formation of presynaptic vesicles, thus assisting in the release of neurotransmitters, such as dopamine. Furthermore, in terms of localization, it can be found not only in neurons, but also in cerebrospinal fluid (CSF) and plasma (Neto, 2016; Ribeiro, 2018).

The gene responsible for the expression of alpha-synuclein is SNCA, which codes for a structure composed of three specific regions that actively contribute to the performance of this protein's functions (Neto, 2016). The regions are called N-terminal, considered amphipathic and capable of interacting with lipid membranes; NAC region (*Non Amyloid-β component*), which is hydrophobic, as it avoids contact with water, thus favoring the aggregation process due to the NAC regions interacting with each other; on the other hand, the C-terminal region, disfavors the aggregation process, as it constitutes an acidic, negatively charged portion (Campêlo, 2017).

However, point mutations, duplications or triplications in the SNCA gene can result in the overexpression of modified chain alpha--synuclein levels in PD, which will form Lewy bodies and develop neurotoxicity. This increase in alpha-synuclein concentration plays an important role in the aggregation process, since monomeric protein structures form oligomers, i.e. peptide chains become polypeptides. Thus, there is a conformational change in the alpha-synuclein which, when aggregated together through the NAC region, results in protofibrils which subsequently give rise to insoluble fibrils, responsible for the formation of intracytoplasmic inclusions, known as Lewy bodies (Poewe *et al.*, 2017).

Given the formation of these corpuscles, there is evidence according to Ribeiro (2018) that these inclusions composed of modified chain alpha-synuclein may alter the substantia nigra due to the association of this protein with the enzyme Tyrosine Hydroxylase, responsible for Dopamine synthesis, thus contributing to the reduction of dopaminergic tone.

Neuroinflammation

The cascade of inflammatory responses seen in PD stems from inflammation mediated through the recognition of alpha-synuclein aggregates, due to the conformational change involved in the expression process, since it is designated as an antigen capable of inducing immune responses in brain tissue (Ransohoff, 2016).

This recognition is determined through surface receptors, i.e. transmembrane *Toll-like Receptors* (TRLs), present in microglia, mainly the TLR2 and TLR4 classes of receptors, which trigger signaling for the pro-inflammatory pathways of the transcription factor NF-kB (*Nuclear Factor kappa-B*) (Rocha; De Miranda; Sanders, 2018).

Therefore, signaling induces the activation of Microglia as well as their respective profiles: Pro-inflammatory, corresponding to M1 and Anti-inflammatory, i.e. M2; it is observed that there is an increase predominantly of M1. These cells are part of the composition of the CNS and are designated as resident macrophages of the brain tissue responsible for maintaining cellular immune homeostasis, acting as phagocytes and releasing various cytokines with high pro-inflammatory potential, which is capable of causing neurotoxicity (Ribeiro, 2018).

Given these functions, the process of activating microglia also includes the secretion of pro-inflammatory mediators responsible for trying to combat Lewy bodies, which are: cytokines, chemokines, proteases, free radicals and prostaglandins (Santana; De Oliveira Silva; Ferreira, 2024). In agreement with this data, studies by Qin *et al*. (2016) have shown that the most common inflammatory mediators that are altered in the blood of PD patients are: TNF (*Tumor Necrosis Factor*), CRP (C-Reactive Protein), the chemokine RANTES (*Regulated on Activation Normal, T-Cell Expressed and Secreted*) and the interleukins (ILs) 6, IL-2, IL-10 and IL-1β, with an emphasis on IL-10, which is considered a commonly increased anti-inflammatory cytokine, given that the others are Pro-inflammatory. However, the same authors state that some of these cytokines actively contribute to the progression of PD, as IL-6, IL-1β and TNF have been shown to cause toxicity in neurons (Qin *et al*., 2016).

It should also be emphasized that proteases (such as Caspase-1) produced by microglia also play an important role in the neuroinflammation process, as they are responsible for promoting an increase in pro-inflammatory cytokines, as they have a proteolytic action capable of cleaving precursor forms of IL-1β, which are released to induce inflammatory responses. However, caspases can also cleave the C-terminal portion of alpha-synuclein, further favoring its change in shape and, consequently, aggregation, as it is a region responsible for preventing constant aggregation. In this way, a cyclical process occurs where the more aggregation, the greater the number of inflammatory responses, consequently developing toxic effects for dopaminergic neurons (Olanow; Kordower, 2017).

Thus, through the hypotheses related to pathophysiology and the forms of diagnosis commonly used in medical practice, it is observed that PD can also be confused with other neurological diseases of a progressive nature, such as SWEDDs (*Scans Without Evidence of Dopaminergic Deficit*), Dementia with Lewy Corpuscles and Tauopathies (Silva *et al.*, 2021).

Thus, the current diagnosis is based mainly on the observation of signs and symptoms that have already been consolidated and described for many years, which affects the decision to diagnose PD, however, it is necessary to understand other more accurate diagnostic methods (Zhang *et al*., 2018). In this sense, it is necessary to use the triad of clinical, neuroimaging and molecular diagnostic techniques, emphasizing the main biomarkers tested, which can establish a better prognosis for the disease (Pinheiro *et al.*, 2024).

DIAGNOSTIC METHODS

The process of specific diagnosis in PD is considered an important factor, to the detriment of the vast access to techniques that are routinely employed, since it is through these that requirements and procedures that can suggest the presence of Parkinson's have currently been established. Therefore, with technological advances in the field of diagnostic medicine, it is important to use analysis methods that can contribute to defining the patient's condition. Therefore, the diagnosis of PD is based on clinical examinations, neuroimaging and biomarkers, which help to identify the characteristics of the disease (Brandão, 2022).

CLINICAL DIAGNOSIS

The clinical diagnosis of PD is one of the greatest challenges in medical practice, since the signs and symptoms presented during the course of the disease can be confused with various parkinsonian disorders (Silva *et al.*, 2021).

To this end, criteria are usually established according to the presence of one or more symptoms presented by the patient. One of the major diagnostic methods comes from the *UK* Parkinson's *Disease Society Brain Bank*, which divides the diagnostic criteria into 3 groups: Necessary criteria for diagnosing PD - corresponding to the presence of one or more pathognomonic symptoms, such as rigidity, tremor and bradykinesia; Negative criteria for PD - which is observed by reporting the patient's clinical history (if there has been any severe head trauma, supranuclear gaze palsy, stroke, among other injuries), so as not to suggest other parkinsonian conditions; Positive support criteria for the diagnosis of PD, where the patient needs to present 3 or more conditions (unilateral onset, rest tremor, progressive disease) to be diagnosed with PD (Parmera et al., 2022).

On the other hand, the system for assessing motor symptoms, such as the Hoehn and Yahr Scale (HY), is used universally to express and classify the degree, i.e. the stage the patient is at, according to the progression of the disease (Cordeiro de Faria et al., 2020; Bhidayasiri; Martinez-Martin, 2017). As such, it is considered the oldest scale for assessing PD, since it was created by Margaret Hoehn and Melvin Yahr in 1967, establishing stages from 1 to 5 according to the symptoms presented by the patients, corresponding to motor disabilities, as seen in table 1 (Opara *et al.*, 2017).

Therefore, according to Modestino *et al.* (2018), the interpretation of the diagnosis is made through the characteristics that the patient presents, being assigned the number related to the stage. Thus, stages 1 - 3 are designated as minimally disabled, while 4 and 5 are designated as severely disabled (Modestino *et al.*, 2018).

In addition to this scale, there is also the UPDRS (*Unified Parkinson's Disease Rating Scale*) which allows the assessment not only of motor characteristics, but also of the daily activities performed by the patient through clinical reports and observations (Santos et al., 2021). This same scale consists of 42 items contained in 4 subscales (I, II, III, IV), which determine, for example, motor and behavioral assessments, daily activities and possible complications in therapy, as shown in Table 2 (Bhidayasiri; Martinez-Martin, 2017).

Sub-scales	Evaluation	Methodology
Sub-scale I	Mental state, behavior and mood	Interview
Sub-scale II	Day-to-day activities	Interview
Sub-scale III	Motor test	Neurological examination
Sub-scale IV	Complications of therapy	Interviews and Observations

Table 2 - Determination of assessments using the sub-scales included in the UPDRS.

Source: Bhidayasiri; Martinez-Martin, 2017.

Thus, according to an updated version of the UPDRS, called the MDS-UPDRS (*Movement Disorder Society-Unified Parkinson's Disease Rating Scale*), Martinez-Martin *et al.* (2018) pointed out that by linking the two scales (HY and MDS-UPDRS) there is a significant increase in the reproducibility of the criteria, being complementary and favoring the diagnosis. However, when evaluating only the HY scale, it was possible to observe that there is a deficit in the criteria, due to its categorization of only motor symptoms, as they do not address non-motor symptoms, thus characterizing the scale as non-specific for diagnosis (Martinez-Martin *et al.*, 2018).

In line with these results, it can be seen that there is a complete relationship between the criteria established by Brasil (2017) and PD, so that parameters are presented from the historical aspects related to the clinic of possible neurological impairments that can interfere in the evaluation to the symptoms of the disease and, concomitantly, its progression.

Classification	Research	Criteria
Stage 1	Unilateral disease	Tremors affect one side of the body, as well as one of the upper or lower limbs.
Stage 2	Bilateral disease	Tremors affect both sides of the body, both upper and lower limbs.
Stage 3	Moderate Postural Instability	Mild bradykinesia, difficulty standing or walking in a straight line.
Stage 4	Severe Postural Instability	Marked bradykinesia and frequent rigidity, inability to carry out daily tasks.
Stage 5	Locomotion Dependent	Total impairment of movement, inability to take care of oneself and to stand.

Table 1 - Classification of the HY scale stages for PD.

Source: Prepared by the authors and adapted from Parkinson, 2016.

However, the studies pointed out by Bhidayasiri and Martinez-Martin (2017), Modestino *et al*. (2018), determine that the use of scales such as the HY, which evaluate the motor conditions of the individual with Parkinson's, can characterize a faster effective diagnosis so that they present degrees, that is, the stages of progression of the disease, as well as the conditions of severity under which the patient finds himself. In addition, the results of recent studies carried out by Martinez-Martin *et al*. (2018) show that there is still a need to associate the HY scale with the UPDRS or the current MDS-UPDRS version, so that there are greater possibilities of determining the disease, since they include greater access to the activities and behaviors experienced by the patient suffering from PD.

However, it is possible to see that there are gaps to be filled with regard to these clinical diagnostic methodologies, since the symptoms presented can corroborate and be confused with the presence of other neurological disorders, thus being non-specific techniques that suggest, but do not confirm the diagnosis because they do not show the mechanisms that culminated in the development of the signs and symptoms, thus requiring more specific diagnostic techniques, such as neuroimaging and molecular (Beserra et al., 2024; Lima et al., 2024; Mattar et al., 2024).

NEUROIMAGING DIAGNOSIS

In the field of diagnosis through neuroimaging techniques used to assess PD, Magnetic Resonance Imaging (MRI), for structural assessment, and *Single Photon Emission Computed Tomography* (SPECT), used to determine functional aspects at a neurological level, stand out. The use of these techniques has strongly contributed to the differential diagnosis of the disease, as they have high accuracy and sensitivity (Samson; Noseworthy, 2022).

In this sense, MRI is considered a commonly used method in the routine identification of PD, as it is able to help differentiate patients who have Parkinson's from those who have developed other neurological disorders associated with Parkinsonian Syndromes (or Parkinsonism), due to its high specificity in detecting microstructural changes (Śmiłowska *et al.*, 2021).

This corroborates the studies by Reneman *et al*. (2021), who point out that neuromelanin deficits, determined by dopaminergic degeneration of the mesencephalic tissue, can be captured, making them visible to MRI, due to the small amounts - microstructures - of neuromelanin being sensitive to the detection attributes of MRI.

In addition to this modality, there is also the possibility of associating MRI with a *Positron Emission Tomography* (PET) technique, which consists of a hybrid exam called PET--MRI, which evaluates soft anatomical structures and concomitantly the functionality of the region studied, It is determined through

the identification of cerebral hypocaptation derived from the administration of the radiopharmaceutical Fluordesoxyglucose (FDG), which contains the radionuclide Fluor-18 (^{18}F), playing a role in the decrease in glucose metabolism evidenced mainly in the nucleus of the putamen base of patients with PD (Leung; Strudwick, 2024).

In relation to the functional assessment of the disease, SPECT is considered to be one of the most promising techniques compared to the other neuroimaging techniques already mentioned, in terms of detection capacity, as well as the prevalence of high sensitivity and specificity (Almeida, 2016). The use of this technique occurs through the increase of a radiotracer, usually associated with a radionuclide, such as^{99m} Tc-TRODAT-1, which has physicochemical characteristics similar to Dopamine Transporters - present in the presynaptic terminals of dopaminergic neurons, which capture dopamine - being responsible for assessing the correlation between the production and effective transport of this respective neurotransmitter (Arena *et al.*, 2021; Hsu *et al.*, 2020).

According to Lin *et al.* (2018),^{99m} Tc-TRODAT-1 SPECT can be useful in detecting the degeneration of dopaminergic neurons, helping to examine the severity of the depletion of these neurons. Furthermore, it is noted that it comprises a technique that has a positive cost-benefit ratio, as well as being appropriate for the diagnosis of patients suffering from PD (Reis *et al.*, 2021).

In this context, the studies presented by Manchanda *et al.* (2024) show that^{99m} Tc-TRODAT-1 SPECT has the property of differentiating patients with PD from healthy patients, so that it is possible to investigate the presence of hypocaptation in the images, resulting from the impediment in the degeneration of neurons, given that^{99m} Tc-TRODAT-1 has an affinity for dopamine transporters. These findings, in turn, consolidate the studies carried out by Pittion Rissardo and Caprara (2023), which showed that the striatal uptake rate of the radiotracer is higher in healthy individuals than in PD patients, thus establishing the normal functionality of dopaminergic neurons.

Thus, it was observed that even though there are some obstacles between the techniques mentioned, such as the presence of artifacts used in MRI or even the difficulty still existing in differentiating Parkinson's from other motor disorders, through SPECT, there is a promising correlation that manages to cover both clinical and imaging diagnosis, since it is noticeable how one is complementary to the other, without extinguishing the importance of both for a more appropriate diagnosis.

MOLECULAR DIAGNOSIS

Given the data discussed, it is clear that PD, despite using clinical diagnosis, can be better elucidated with other diagnostic techniques in conjunction (Júnior *et al.*, 2023). In this sense, according to Cabreira and Massano (2019) there are factors in PD that present a heterogeneous epitopathogenesis, which is related to the genetic-environment interaction, thus the use of genetic tests and other techniques to identify pathogenic *loci* is growing, due to a good cost-efficiency ratio. This information can be used to study and use biomarkers, which are molecules that indicate normal or pathogenic biological processes, which in this sense are currently necessary in an attempt at early detection in the diagnosis and prognosis of PD, focusing on studies with biofluids (cerebrospinal fluid (CSF), blood cells and urine) (Júnior *et al.*, 2023; Polissidis *et al.* 2020).

Regarding the use of blood, Costa *et al.* (2018) determined that it is a useful source of analysis, since it has a positive cost-benefit ratio, due to the extraction of the genome, through the circulating leukocytes in the

peripheral vessels. From this material, specific genes can be obtained for the detection of genetic biomarkers resulting from mutations present in the course of PD, such as the SNCA genes (present in the PARK 1 and PARK 4 *loci*, responsible for altering alpha-synuclein), GRA, PARKIN, LLRK2, DJ1 and the PINK1 gene (Lotankar; Prabhavalkar; Bhatt, 2017).

In view of this search for specific genes, which were presented above, it is known that more than 10 genes related to the causes of susceptibility to PD have been identified, which have great heterogeneity when expressed. Thus, 10% of individuals with PD pass on the genes hereditarily, causing dominant (PARK1, PARK3, PARK4, PARK5, PARK8 (the same as LRRK2), PARK11 and PARK13) or recessive (PARK2 (PARKIN), PARK6 (PINK1), PARK (DJ-1), PARK9 and PARK13), while only 5% come from sporadic mutations, being monogenic or Mendelian, which characterizes a mutation by a single alteration of a gene (Gonçalves *et al.*, 2018).

It should also be noted that the studies by Batistela *et al.* (2016) and Costa *et al.* (2018) are related to the use of *microRNAs* (miRNAs), as they are found in the blood, specifically in the plasma of PD patients. These miRNAs can be used as genetic biomarkers, detected through Molecular Biology techniques such as *Microarray* or RT-qPCR (*Reverse Transcription Polymerase Chain Reaction quantitative Real Time*) associated with a set of bioinformatics analyses. The relationship between these authors also corresponds to the accuracy of 91% sensitivity and 100% specificity of the miRNAs: miR-1826, mi-450 b-3p, miR 626 and miR-505; so that it configures a very effective analyte for the early detection of PD (Batistela et. al., 2016; Costa et. al., 2018).

Transposing this idea, authors such as Kwon *et al.* (2022) determine an important biochemical component that is present in the CSF of patients with the disease: the proteins o/t-α-syn (Total oligo/alpha-synuclein, i.e. the total concentration of alpha-synuclein oligomers) and Aβ42/tau; which help in the diagnosis of PD. This approach, in turn, solidifies the data pointed out by Vivacqua *et al.* (2016), who reported the presence of high levels in the CSF of modified-chain *alpha-synuclein*, as well as its total fraction called *t-α-synuclein*. Through these conditions, which culminate in the detection of proteins related to the progression of PD, the use of CSF is observed to contribute as a potentially effective sample in obtaining information derived from the deleterious effects present in Parkinson's (Hatano *et al.*, 2024).

However, there are other analyte profiles, i.e. biomarkers at biochemical levels that can effectively help in the conceptions that permeate the diagnosis of PD, among which can be mentioned the decrease of amino acids in the serum of these patients, such as: alanine, arginine, threonine and phenylalanine; which are the result of oxidative stress mechanisms or mitochondrial dysfunction, which are involved in the progression of the disease. It should be noted that these amino acids can be detected using the *High Performance Liquid Chromatography* (HPLC*)* technique (Socha; Koba; Kośliński, 2019).

In addition to these, there is also the DJ-1 protein, which is expressed by the PARK7 gene and is associated with natural distribution in brain tissue. However, in PD this protein is elevated, due to the oxidative stress mechanisms produced by the patients. However, analytical factors that can contribute to false positives should be considered, due to possible hemolysis or the presence of red blood cells in the plasma or CSF, since the DJ-1 protein is present in erythrocytes (Lind-Holm Mogensen *et al.*, 2023).

In contrast, Azevedo (2018) proposes the use of this same protein, being detected through saliva - specifically from the subman-

dibular glands - where an increase was found that contributed significantly to the detection in the progression of the disease, as it is believed that samples obtained through saliva, to assess DJ-1 concentrations, can progressively minimize analytical errors, in terms of false--positive results.

Another commonly used biomarker is neuromelanin, which is a dark pigment found in dopaminergic neurons and is responsible for storing iron. This protein has great relevance in association with the MRI imaging technique, since its detection is noticeable to the detriment of the decrease evidenced by the death of these neurons, thus making it an important biomarker for PD (Lotankar; Prabhavalkar; Bhatt, 2017).

The onset of PD pathology probably occurs long before the first characteristic motor symptoms. Thus, the use of biomarkers for the diagnosis of PD may be a potential requirement for detecting the disease, especially in the early stages of the disease process, making it possible to establish a greater affinity in relation to Parkinson's disease (Costa *et al.*, 2018).

CONCLUSION

Studies into PD are promising because they provide important evidence about genetics, by discovering genes and expressions of certain proteins that are biochemically present in the course of the disease. In addition, these studies also show a strong relationship between the use of possible genetic and biochemical markers and neuroimaging techniques - which determine the structural and functional behavior of the disease - as well as the use of scales that assess the motor conditions and daily functions performed by patients living with Parkinson's disease.

Therefore, the evolution of research in this study suggests that the diagnosis currently established and used is related to clinical evidence, through motor assessment scales. Diagnosis by neuroimaging and biomarkers present previous evidence that indicates the presence of PD, before the signs and symptoms appear, but both diagnostic approaches are not fully disseminated and used due to the need for more studies on their applicability in detecting the disease. Despite this, correlating the three forms of diagnosis offers great possibilities for discovering patients with PD, so that they can offer a better quality of life to those affected by this disease.

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