α-Synuclein Aggregates and Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is characterized by the progressive degeneration of dopaminergic neurons of the substantia nigra, leading to motor changes that progress to tremors, rigidity, and bradykinesia with postural instability. Over time, cognitive disorders such as mild dementia, emotional changes such as depression and anxiety, autonomic and sleep disorders are observed. It is the second most prevalent neurodegenerative disease among the elderly population, and is a chronic and progressive clinical condition. It is currently classified as a synucleinopathy, belonging to a group of diseases characterized by anomalous deposition of the alpha-synuclein protein. This protein aggregates abnormally in neuronal tissue, giving rise to Lewy bodies. α-synuclein is a soluble protein of 140 amino acids that appears abundantly in the synaptic terminals of neurons. The sequence of terminal N amino acids from 1-60 is composed of several lysines and these repeats appear to be important for interaction with vesicle lipids. The central sequence that surrounds the amino acid residues 61-95 is the most hydrophobic portion of the protein, being known as the non-amyloid beta component, capable of changing its state from helix to pleated beta sheet, exposing the hydrophobic groups and favoring protein aggregation. The 96-140 residues of the terminal C are mainly made up of acidic, negatively charged amino acids, which are necessary for calcium binding. The pathogenic mechanisms of PD involve incorrect folding and aggregation of α-synuclein, failure of the metabolism of these proteins due to deficiency in the proteosome/ubiquitin or phagolysomal system, mitochondrial dysfunction, inflammation, and oxidative stress. Most cases of Parkinson's are characterized by being sporadic in nature, corresponding to about 90-95%. The monogenic forms may be recessive or dominant, consisting of only 30% of familial cases and accounting for only 3-5% of sporadic cases.

Keywords: Neurodegenerative, Synucleinopathy, Amyloidosis, Pleated Beta.

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INTRODUCTION

Parkinson's disease (PD) is an adult-onset progressive neurodegenerative disorder, first described as "agitation paralysis" by James Parkinson in his 1817 essay on Acute Paralysis. The pathogenesis of the disease remained unclear until the beginning of the 20th century, when the German pathologist Frederick Lewy, in 1912, described neuronal cytoplasmic inclusions in several brain areas. Subsequently, in 1919, Tretiakoff observed that the loss of neurons in the substantia nigra pars compacta (SNc) region of the midbrain was the most relevant abnormality in PD. In the 1950s, researchers identified the relevance of dopamine and its deficiency in the basal ganglia as the key element for understanding the pathophysiology and pathological biochemistry of PD (Hornykiewicz, 2006).

It is the second most prevalent neurodegenerative disease among the elderly population, and is a chronic and progressive clinical condition. Such a pathological condition is attributed to the significant reduction of the neurotransmitter dopamine in the basal ganglia of the central nervous system (Cabreira, Massano, 2019).

It is currently classified as a synucleinopathy, belonging to a group of diseases characterized by anomalous deposition of the alpha-synuclein protein. In PD, this protein aggregates abnormally in neuronal tissue, giving rise to Lewy bodies, which represent a distinctive pathological feature of this group of diseases (Spillantini *et al.*, 1997).

PD is characterized by motor symptoms, such as tremors, muscle stiffness, bradykinesia, and postural instability, resulting from the progressive degeneration of nerve cells that produce dopamine in a region of the brain called the substantia nigra. In addition to motor symptoms, PD can also present expressive non-motor manifestations. These include cognitive disorders, such as the occurrence of mild dementia, emotional changes, notably depression and anxiety, as well as autonomic disorders, sleep disorders, and autonomic dysfunction (Hayes, 2019). This wide variety of non-motor symptoms considerably affects patients' quality of life, exacerbating the impacts of the disease comprehensively and making diagnosis and clinical management challenging.

PATHOPHYSIOLOGY

The basal ganglia are a collection of gray matter structures named for their deep location within the anterior part of the brain. Functionally, they play a significant role in controlling posture and voluntary movements through connections with the thalamus, cortex, and neighboring structures. In addition, the basal ganglia have connections to the pathways of the limbic system, which govern the expression of the various behaviors and motivational states (Drake; Vogl; Mitchell, 2021).

The following structures are components of the base nuclei:

a) of the telencephalon: caudate nucleus, putame, globus pallidus and nucleus accumbens;

b) midbrain: substantia nigra (compact and reticular parts);

c) diencephalon: subthalamic nucleus.

It is also worth mentioning the existence of structures correlated to the basal nuclei, such as the ventral tegmental area, the peduncle-pontine nucleus, the dorsal raphe nuclei and the habenula (Meneses, 2011). The striatum is located laterally to the thalamus and is almost entirely divided by a band of nerve fibers, the internal capsule, in the caudate and lentiform nuclei. The striated nomenclature is used because of the striated appearance produced by the gray matter cords that run through the inner capsule and connect the caudate nucleus with the putame of the lentiform nucleus (Splittgerber, 2021).

The caudate nucleus lies medially to the inner capsule, in a large C-shaped mass of gray matter, which is divided into head, body, and tail, which closely follow the shape of the lateral ventricle. The head of this nucleus has a rounded shape that contributes to the formation of the lateral wall of the anterior horn of the lateral ventricle. Also at this level, the head of the caudate nucleus is continuous with the putame. Because of this proximity, the putame and caudate nucleus are called the striatum. At the level of the interventricular foramen, the head of the caudate nucleus transforms into the body, which is long, and thins as it is directed towards the tail. Along its path, your body contributes to the floor of the lateral ventricle. Near the posterior margin of the thalamus, the body of the caudate nucleus to the tail segment. It continues anteriorly, within the roof of the inferior horn of the lateral ventricle, to terminate in the amygdaloid body (Drake; Vogl; Mitchell, 2021).

The lentiform nucleus is a mass of gray matter whose broad convex base is directed laterally, while the narrower end is directed medially. It is embedded in the white matter of the cerebral hemisphere and related medially to the internal capsule, which separates it from the caudate nucleus and thalamus. Laterally, it is related to a thin sheet of white matter, the outer capsule, which separates it from a thin sheet of gray matter, called the cloister. In turn, the claustrum separates the outer capsule from the subcortical white matter of the insula. A vertical plate of white matter divides the nucleus into a larger, darker lateral part, the putame, and a lighter inner part, the globus pallidus. The pallor of the globus pallidus is due to the presence of a high concentration of myelinated nerve fibers. Inferiorly, at its anterior end, the putame is continuous with the head of the caudate nucleus (Splittgerber, 2021).

The amygdaloid body is located in the temporal lobe, close to the uncus, is considered part of the limbic system and through its connections, can influence the body's response to environmental changes. For example, in the presence of a feeling of fear, it can modify heart rate, blood pressure, and respiratory rate (Splittgerber, 2021).

The substantia nigra is a dark-colored structure, formed by neurons containing melanin, and which is located in the midbrain, between the tegmentum and the base of the peduncle, which are components of the cerebral peduncle. It is classified as the largest nuclear structure of the midbrain, being interposed between the subthalamic nucleus and the base of the peduncle. The substantia nigra is divided into 2 parts: the pars compacta (SNc) and the pars reticulata (SNr). The pars compacta is located dorsally, and its neurons contain large amounts of dopamine. This division of the substantia nigra presents the main efferent projections, especially through the nigrostriatal fibers, which make the connection between the striatum and are involved in the control of movements. There are also connections between the amygdala (involved with emotions and motivation) and the reticular formation (involved with wakefulness) with the pars compacta of the substantia nigra. The pars reticulata, in turn, located ventrally, receives the main afferent projections for the substantia nigra, coming mainly from the striatum: striatonigral fibers, and the neurotransmitter involved is GABA (gamma-aminobutyric acid) (Meneses, 2011). The substantia nigra has three different types of neurons classified according to their shape, degree of pigmentation, types of cellular processes, and cell size. Type I neurons are larger, found in *the pars compacta*, and their cell body pole contains large amounts of neuromelanin granules. Type II neurons are medium-sized, found in the *pars reticulata* and *pars diffusa,* but are in small numbers in *the pars compacta*. This neuron does not have neuromelanin deposits, but it does have lipofuscin granules. Type III neurons are usually small, found in the *pars diffusa,* and lack lipofuscin granules (Di Lorenzo, 2011).

The activity of the basal ganglia is initiated by information received from the premotor and supplementary areas of the motor cortex, the primary sensory cortex, the thalamus, and the brainstem. The efferent flow from the basal ganglia is conducted through the globus pallidus, which then influences the activities of the motor areas of the cerebral cortex or other centers in the brainstem. Consequently, they control muscle movements by influencing the cerebral cortex and do not exert any direct control through descending pathways to the brainstem and spinal cord. In this way, the basal ganglia help in the regulation of voluntary movements and in the learning of motor skills, such as writing the letters of the alphabet, drawing a diagram, kicking a soccer ball, using the vocal cords to speak and sing, and using the eye muscles when looking at an object (Splittgerber, 2021).

These structures influence not only the execution of a certain movement, such as the movement of the limbs, but also help to prepare them. This can be achieved by controlling the axial and cingulate movements of the limbs, and positioning their proximal portions. The activity of certain neurons of the globus pallidus increases before the execution of active movements in the distal muscles of the limbs. This important preparatory function allows the trunk and limbs to assume

appropriate positions before the primary motor part of the cerebral cortex activates distinct hand and foot movements (Splittgerber, 2021).

There are efferent pathways that project from the striatum in a converging direction to influence the basal ganglia nuclei. The so-called indirect pathway is responsible for causing the disinhibition of cells in the subthalamic nucleus from a series of inhibitory signals coming from the putamen and the external pallidal segment. There is the release of subthalamic neurons that transmit excitation to neurons of the internal pallidal segment, which, in turn, provide inhibitory impulse to the motor nuclei of the thalamus, resulting in a decrease in thalamic activation in the motor cortex and smoothing of cortically initiated motor activity. However, when this pathway presents some dysfunction, the neurons of the thalamic motor nuclei are not inhibited, allowing the excitation of the motor cortex and resulting in the production of involuntary movements that cannot be stopped. Neurons in the indirect pathway express dopaminergic receptors (D2), in which dopamine acts as an inhibitory (Freeze, 2013; Guyton & Hall, 2017).

This pathway is responsible for the stimulation of the cortex (via glutamatergic neurons) and the conduction of inhibitory neurons in the putamen to cells of the inner pallid segment, which project to the motor nuclei of the thalamus. The neurons in the inner segment form an inhibitory circuit that surrounds the thalamocortical neurons that project into the motor cortex, causing the neurons to be disinhibited, thus allowing the transmission of excitatory impulses from the thalamus to the motor cortex and consequently movement. (Freeze, 2013; Guyton & Hall, 2017).

The movement abnormality seen in PD is caused by degeneration of the dopaminergic nigrostriatal projection, leading to akinesia (poverty of movement), bradykinesia (slowness), muscle rigidity, resting rate tremor (Wichmann, DeLong, 2007). In PD, there is a decrease in the activity of the direct pathway, which is inhibitory, in parallel, there is an increase in activity in the so-called indirect pathway, which is "non-inhibitory" (inhibits the direct pathway, which is inhibitory). The effect of this imbalance is an increase in the firing rate of inhibitory neurons in the globus pallidus internamus, with references to premotor structures such as the thalamus. Inhibition of the premotor centers explains the symptoms of akinesia/bradykinesia, but does not explain tremor and rigidity. Movement disorders in PD disease are commonly associated with slow oscillations and increased synchrony of neuronal activity in the basal ganglia. Inhibitory stimuli from the striatum to the external globus pallidus is a key parameter to control oscillations in the basal ganglia (Kumar *et al.,* 2011).

The pathophysiological aspects of PD are the progressive degeneration of myelinated neurons of the substantia nigra compacta (SNpc) and the presence of cytoplasmic inclusions, called Lewy corpuscles, which are formed by α-synuclein and ubiquitin.

The degeneration of dopaminergic neurons of the nigrostriatal pathway leads to a high reduction of dopamine levels in the striatum, as well as in other basal ganglia. The basal ganglia are considered a modulating lateral loop that guides the flow of information from the cerebral cortex to the motor neurons of the spinal cord. Cortical motor areas project in a somatotopic manner into the striatum, establishing glutamatergic excitatory synaptic connections with GABAergic neurons in the middle spinous region. In the direct pathway, neurons project monosynaptically to the SNpr and to the inner segment of the globus pallidus; These, in turn, relay to the anterior ventral and lateral ventral thalamus. Since the neurotransmitter of both bonds is GABA, which is inhibitory, the final effect of direct pathway stimulation is an excitatory boost to the cortex. In the second pathway, called indirect, gabanergic neurons project to the outer segment of the globus pallidus, thence to the subthalamic nucleus, and finally to the globus pallidus inner. However, this final binding of the subthalamic nucleus to the globus pallidus interlimus and SNpr is an excitatory glutamatergic pathway. Therefore, the final effect of indirect pathway stimulation at the level of the striatum is to reduce excitatory efflux from the thalamus to the cerebral cortex. The main aspect of this model of basal ganglia function, which is responsible for the symptoms observed in PD, is the differential effect of dopamine from the substantia nigra compacta (SNpc) on the direct and indirect pathways. The neurons in the striatum that give rise to the direct pathway express excitatory D1 receptors, while the neurons that form the indirect pathway primarily express inhibitory D2 neurons. Thus, the dopamine released in the striatum tends to increase the activity of the direct pathway and reduce that of the indirect pathway, while the depletion that occurs in PD has the opposite effect. The final effect of the reduction of dopaminergic influx in PD consists of a marked increase in the inhibitory efflux of the SNpr and the globus pallidus interna to the thalamus and a reduction in the excitation of the motor cortex (Gonçalves, 2021). In PD, at the macroscopic level, the brain may present a slight atrophy of the frontal cortex, with ventricular dilatation. The main morphological change is observed in the brainstem, with loss of a dark pigmented area in the substantia nigra, corresponding to the death of dopaminergic neurons (Kouli *et al*., 2018).

Thus, the loss of dopaminergic neurons is associated with the onset, albeit slow, of motor symptoms, and there is a direct relationship between the duration of the disease, the extent of dopamine loss, and motor dysfunction. The classic motor symptoms of PD are bradykinesia, resting tremor, muscle rigidity and postural instability, and these only manifest when there has already been a loss of about 60% of the nigral neurons and depletion of 80% of the dopamine content of the striatum. Non-motor symptoms such as cognitive deficits, sleep disturbances, olfactory dysfunction, and depression are other common disabling manifestations of the disease (Gonçalves, 2021).

The neuropathological characteristics for the onset of motor symptoms in PD are related to the degeneration of dopaminergic neurons, or to the loss of dopaminergic terminals in the basal ganglia, as pointed out more recently (Simon *et al.*, 2020).

Although the symptoms of PD are well characterized, the underlying mechanisms and causes of the disease are still not fully understood. Pathogenic genetic mutations in genes such as α-synuclein, parkin, PINK-1, and LRRK-2 can lead to familial forms of PD. Environmental factors such as heavy metals, pesticides, and fungicides have also been associated with a high risk for the disease (Gonçalves, 2021).

CHARACTERISTICS OF THE A-SYNUCLEIN PROTEIN

Protein aggregation occurs due to changes in their secondary levels, modifying their solubility and favoring their deposit. Various pathologies, with different intensities and organs or systems, are related to the incorrect folding of proteins (Covizzi, et al. 2023). Parkinson's disease (PD) is characterized by the emergence of intracellular inclusions of a protein called misfolded α-synuclein, forming aggregates in fibrils that relate to the loss of dopaminergic neurons in the brain (Bridi, Hirth, 2018).

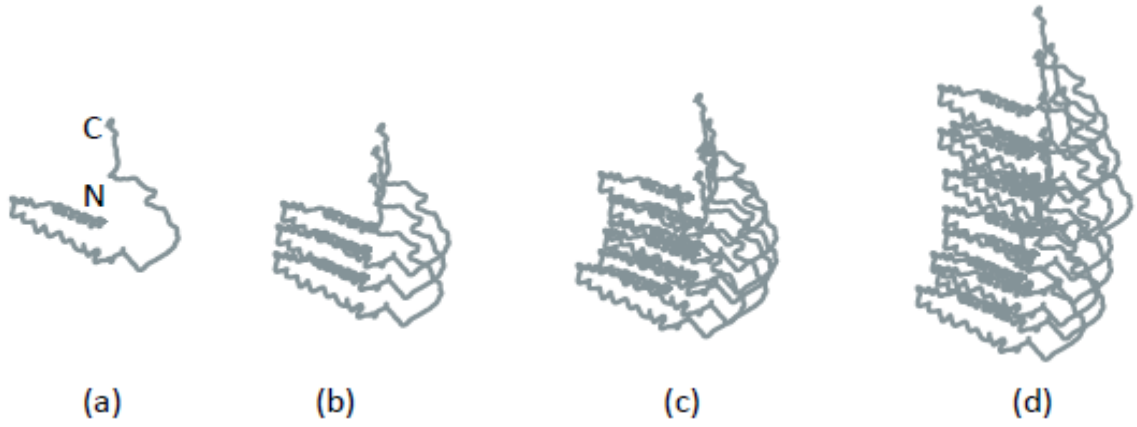
α-synuclein, encoded by the SNCA gene located at 4q22.1, is a soluble protein of 140 amino acids that appears abundantly in the synaptic terminals of neurons (Xu *et al.*, 2015). Its structure is characterized by seven repeats of 11 amino acids in the N-terminal sequence, being highly conserved between the isoforms of β and γ-synuclein. This region of the protein has an amphiphilic nature, being involved in binding to the membrane bilayer of synaptic vesicles (Whittaker *et al.*, 2017). The amino acid sequence from 1-60 of the terminal N has several lysines and these repeats seem to be important for the interaction with the lipids of the gallbladder. The central sequence that surrounds the amino acid residues 61-95 is the most hydrophobic portion of the protein, being known as the non-amyloid beta component (NAC), capable of changing its state from helix to pleated beta sheet, exposing hydrophobic groups and favoring protein aggregation. The terminal C region is much less conserved and has an acidic nature in composition (Sulzer, Edwards, 2019). The 96-140 residues of terminal C are mainly made up of acidic amino acids, with a negative charge, necessary for calcium binding (Guerrero-Ferreira *et al.*, 2020). A serine 129 residue from this region can undergo phosphorylation (Gallegos, *et al*. 2015). Studies have confirmed that S-129 participates in the regulation of α-synuclein involving association with membrane structures (inhibitory effect), is involved in protein-protein interactions, seems to be related to synaptic plasticity, nuclear translocation, interaction with metal ions, and participates in turnover for protein degradation (Fricova *et al.*, 2020).

Figure 1: Representation of the sequence of 140 amino acids of α-synuclein divided into 3 regions: The N-terminal region (1 – 60) has several residues of the basic amino acid lysine (positively charged). The central region (amino acids 61 – 95) is composed of nonpolar waste and is known as the non-amyloid component (CNA). The unconserved C-terminal region (amino acids 96 – 140) has 14 acid amino acids (negatively charged) that constitute a calcium binding site.

Non-terminal (A1 – A60)	CNA (A61–A95)	C-Terminal (A96 – A140)

Post-translational modifications such as phosphorylation, ubiquitination, nitration, O-N-acyl-glycosylation, and protein truncation play important roles in aggregation, facilitating the formation of α-synuclein inclusions (Zhang *et al.*, 2019). Under normal physiological conditions, α-synuclein monomers function in dynamic equilibrium between the soluble cellular or membrane-bound form. Under stress or pathological conditions, α-Syn monomers can interact with each other forming oligomers that favor the formation of protofibrils, causing the formation of β-amyloid leaf fibrils, which aggregate into structures known as Lewy bodies (Bridi, Hirth, 2018). According to studies by Ingelsson (2016), α-synuclein aggregation possibly begins with a conformational change in the monomeric shape of the protein, followed by the gradual formation of oligomeric protein species. The author suggests that these soluble aggregates are the most toxic form of α-synuclein. Such species, as well as the fibrils already formed, potentiate the process for the formation of additional aggregates, characterizing a cascade of reactions.

Figure 2: Schematic representation of α-synuclein showing the monomeric unit with its terminal N and C regions (a). The aggregation of some units forms an oligomer (b), which can continue to aggregate to form protofibrils (c) and amyloid fibrils (d).



The post-translational modifications that occur in the cytosol, such as phosphorylation, ubiquitination, nitration, O-N-acyl-glycosylation, and protein truncation play important roles in facilitating the formation of α-synuclein inclusions (Zhang *et al.*, 2018). The mechanism by which α-synuclein aggregation leads to toxicity and causes apoptosis involves a series of events that begins with the formation of oligomers and mature fibrils. (1) The formation of Lewy bodies and neuronal deposits deplete these vital components in the cell, (2) mitochondrial impairment occurs, since the altered α-synuclein translocates to the mitochondria, favoring the generation of reactive oxygen and

nitrogen species, causing oxidative stress, leading to a compromise in the production of ATP. The damage generated in the mitochondria promotes the release of cytochrome C, activating the mitochondria to initiate the apoptotic process. (3) Changes occur in the endoplasmic reticulum with inhibition of protein trafficking due to ATP depletion and an increase in calcium release. (4) Pores are formed in the membrane presumably due to the penetration of toxic forms. This alters the permeability, promoting the influx of calcium and other ions into the cytosol. (5) The adhesion of α-synuclein aggregates to the lysosome membrane alters chaperone-mediated autophagy, compromising the proteosomal system. (6) The release of α-synuclein aggregates into the extracellular space by damaged neurons interferes with the activity of adjacent neurons, activating intracellular aggregation and synaptic deficiencies. (7) These α-synuclein oligomers activate the hyperphosphorylation of the Tau protein, a component of microtubules, impairing cell transport and increasing toxic aggregation in the cytosol. (8) The presence of α-synuclein aggregates at the terminals reduces the release of synaptic vesicles. (9) There is an impairment in dopamine metabolism, inducing the formation of reactive oxygen species (Manzanza *et al.*, 2021).

STRUCTURAL ALTERATIONS OF A-SYNUCLEIN IN PARKINSON'S DISEASE.

The function of α-synuclein in the body has not yet been fully established. From a physiological point of view, α-synuclein appears to be involved with the compartmentalization, storage, and recycling of neuronal neurotransmitters (Zhang *et al.*, 2019). It is not yet known whether α-synuclein binding to membranes can inhibit or promote protein aggregation (Killinger *et al.*, 2019). However, laboratory tests performed by Fanning et al. (2018) showed important changes in the lipid composition downstream of protein aggregates, where neutral lipids prevail. It is not possible to conclude whether the toxicity is caused by these alterations or whether they hinder vesicle traffic.

Mitochondrial dysfunction in Parkinson's disease can be caused by mutation or triplication of α-synuclein, chemicals such as 1-methyl, 4-phenyl, 1,2,3,6-tetrahydropyridine (MPTP), rotenone (insecticide), maneb (agricultural fungicide), mutations in complex I components. After complex I inhibition, electron leakage into the electron transport chain and an increase in reactive oxygen species occurs, leading to activation of intrinsic pro-apoptotic pathways (Bose, Beal, 2016, Ge *et al.*, 2020). Mitochondrial biogenesis is activated by numerous stress signals, such as availability of nutrients, growth factors and hormones, toxins, temperature fluctuations, and oxygen. The process involves not only the production of internal and external membranes, the synthesis of mitochondrial proteins encoded by the nuclear genome and the duplication of mtDNA. Mitochondrial biogenesis is thought to be strongly regulated by the peroxisome proliferator-activated gamma receptor (PPARγ) (Jiang *et al.*, 2019).

The Endoplasmic Reticulum (ER) has several physiological functions, including lipid biosynthesis and storage, protein synthesis and folding and export, calcium regulation and glucose metabolism. It is a dynamic organelle that coordinates metabolic responses to maintain cellular function (Costa *et al.*, 2020). In Parkinson's disease, the presence of toxic α-synuclein with its aggregates causes stress in the ER by altering intracellular protein trafficking, synaptic vesicle transport, and calcium homeostasis. Due to the high concentration of proteins in ER, control of protein folding is critical to maintain normal cell metabolism and functions. Disturbances in this balance can lead to the accumulation of misfolded proteins in the ER that can lead to the collapse of the entire secretory pathway and cellular homeostasis (Colla, 2019).

The binding affinity of α-synuclein oligomers is influenced by the composition of lipids with negatively charged heads. Vesicles containing high concentrations of phospholipids are susceptible to oligomer bonding-induced disruption (Musteikyté *et al.*, 2021). Evidence shows a transient binding of α-synuclein under physiological conditions to the membrane, while the oligomeric form of membrane binding in an excessive manner leads to disruption of membrane integrity. Interaction with vesicles can lead to abnormal clustering and accumulation of synaptic vesicles, altering the release of the neurotransmitter at the synapse. Increased levels of monounsaturated and polyunsaturated fatty acids in the composition of these lipids contribute to the pathological formation of α-synuclein oligomers (Gilmozzi *et al.*, 2020)

Autophagy is an essential catabolic mechanism for the elimination of misfolded proteins and damaged organelles. Autophagy degrades many toxic proteins, preventing the formation of aggregates, as in the case of α-synuclein, decreasing the levels of this toxicity. Defects in these pathways lead to the accumulation of protein aggregates that may be associated with neurodegenerative diseases such as PD (Djajadikerta *et al.*, 2020). The ubiquitin-proteasome system (UPS) and the autophagic-lysosomal (ALP) pathway are able to eliminate overespresses or misfolded proteins, maintaining homeostasis. UPS is the main way to degrade α-synuclein aggregates, and can be assisted by ALP when overloaded. Soluble oligomers of α-synuclein can impede proteosome activity, forming a vicious cycle that further intensifies the accumulation of misfolded proteins (Du, 2020).

Prions consist of misfolded proteins (PrP) capable of inducing normal monomers to transform into aggregates of PrP. In this way, the pathological form of the protein can spread throughout the brain. Bovine spongiform encephalopathy and Creutzfeldt-Jakob disease are infectious neurodegenerative diseases caused by prions. Poorly folded α-synuclein has an effect similar to prions, that is, it is capable of interfering with the folding and aggregation of other proteins, called the "seed" effect (Du, 2020). Several mechanisms for the uptake of α-synuclein fibrils by cells have been proposed, including receptor-mediated endocytosis, liquid-phase endocytosis, vesicles-

mediated systems, or tunneling nanotubes mediating entry. After endocytosis, the fibrils normally travel through the endocytic pathway to the lysosomes. Entering through other pathways, these misfolded proteins probably reach the cytosol, acting on monomeric α-synucleins, transforming them into pathological inclusions (Karpowicz *et al.*, 2019).

Tau protein is a component of microtubules that is concentrated in the labile domain of the axonal microtubule, demonstrating its role in regulating stability. Its aggregation and formation of neurofibrillar tangles from the hyperphosphorylated form is involved in many neurological disorders. These tau-α-synuclein aggregate forms can contribute to cell death and alter axonal transport as well (Zhang *et al.*, 2018).

Toxic forms of α-synuclein accumulate in presynaptic terminals, affecting the release of the neurotransmitter. High levels of misfolded protein alter the size of vesicles and impair traffic. The overexpression of α-synuclein can interfere with the formation of the SNARE (Soluble NSF-Attachment Protein Receptors) complex, which is important for the release of the neurotransmitter, reduces endocytic recovery (Bridi, Hirth, 2018). Oligomeric α-synuclein interferes with the integrity of the pre- and postsynaptic plasma membrane by displacing voltage-regulated calcium channels and N-Methyl-D-Aspartate (NMDA) receptors. These toxic protein interactions lead to an influx of calcium, further stimulating protein aggregation. These effects favor mitochondrial oxidative stress, potentiating cell death (Kulkarni *et al.*, 2022)

Alterations in cellular oxidation-reduction potential, mitochondrial dysfunctions and neuroinflammation are involved in the degeneration processes, especially of dopaminergic neurons. In this context, the presence of dopamine may represent a crucial determinant of neuronal death. (Chakrabarti, Bisaglia, 2023). Both reactive oxygen species and reactive quinones can induce cytotoxic effects, promoting neuronal degradation. The substantia nigra gets its name from the presence of a dark and insoluble pigment, neuromelanin, which accumulates with aging within the autolysosomal organelles. Neuromelanin is the main iron storage site in the nervous system of healthy individuals, existing in a ferritin-like configuration where iron is stored in ferric form (Fe+3) (Esrf, 2023).

GENETIC CONTRIBUTION

Most cases of PD are characterized by being sporadic in nature, corresponding to about 90-95% of the total. Well-established monogenic forms may be recessive or dominant, but are involved in only 30% of familial cases and 3-5% of sporadic cases. Early monogenic causes are consequences of mutations in the genes of α-synuclein (SNCA), Leucine-rich Repeat Kinase 2 (LRRK2), the protein involved in Golgi transport to the plasma membrane and endocytic recycling (SPV35), the parkin protein (involved in the autophagy process), the protein that regulates parkin production

(PRKN) and the putative protein kinase 1 (PINK1) that regulates parkin activity through phosphorylation. Alterations in genes encoding the Tau protein (MAPT), a component of microtubules, and the enzyme glucocerebrosidase (GBA) have been related to the pathology (Klein, Westenberger, 2012; Arkinson, Walden, 2018; Xu *et al.*, 2020).

Mutations that promote gain-of-function in the LRRK2 signaling kinase are related to a notable number of cases of familial and idiopathic PD. This protein is a potential target for therapies that decrease the effects of PD (Azeggagh, Berwick, 2021).

Variants of lysosomal protein-producing genes are believed to be associated with more than half of cases, with the most common genetic risk factor being alterations in the GBA gene, which encodes the lysosomal glucocerebrosidase (GCase) enzyme, which metabolizes sphingolipids (Gegg, 2022).

The involvement of monogenic events in early-onset PD has shown the importance of mitochondrial quality control as a key factor for the development of this disease. Mutations that lead to loss of function in the genes encoding the PINK 1 or Parkin proteins result in insufficient removal of non-functional mitochondria (Miller, Muqit, 2019).

FINAL THOUGHTS

The neurological disorder is the main source of disability in the human population, with Parkinson's Disease being the fastest growing in number of cases, expected to reach a total of 12 million people by 2040 (Dorsey *et al.*, 2018). These are pathologies that involve multiple factors that lead to different clinical manifestations, with genetic contribution and the participation of environmental agents. In PD, in addition to the classic motor symptoms, other manifestations such as rapid eye movement, sleep disturbances, loss of smell, constipation, and depression appear in the prodromal phase, evolving into a set of cognitive impairment (Jankovic, Tan, 2020). Diagnosis is commonly based on medical observations by tests of various motor symptoms, and can be subjective, as they are based on evaluations of movements that are difficult to classify, making diagnosis at an early stage challenging (Mei *et al.*, 2021).

The incorrect folding and subsequent aggregation of a synuclein is believed to play a central role in the death of neurons. The imbalance between the expression and degradation of this protein would lead to a progressive accumulation of synuclein, forming oligomers that favor the fibrillation process. These α-synuclein protofibrils would be toxic to neurons (Michel *et al.*, 2016). Pathogenic mechanisms involve incorrect folding and aggregation of α-synuclein, failure of protein metabolism due to deficiency in the proteosome/ubiquitin or phagolysomal system, mitochondrial dysfunction, inflammation, and oxidative stress (Jankovic, Tan, 2020).

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