

Relevance of mitochondrial alterations in the neurodegenerative diseases, an update and discussion of evidence

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Abstract

Neurodegenerative diseases (ND) are undoubtedly part of the more important health issues worldwide. The loss of independence and decreased quality of life are characteristics of these patients that translate into an economic load on relatives and health services. Although myriad factors or metabolic alterations are blamed as causatives, there is a common defect in almost every ND, mitochondrial dysfunction. Mitochondria are the cell's leading energy supplier; therefore, altering its function will affect the cellular function with the energy demand. Defects in mitochondrial mechanisms such as ATP synthesis by the mitochondrial respiratory chain, mitochondrial dynamics, apoptosis regulation, and oxidative stress are described as part of the pathological characteristics of Alzheimer's, Parkinson's, Huntington's diseases, and Amyotrophic Lateral Sclerosis. In this review, we will briefly describe the mitochondrial roles in cell life before analyzing the recently published bibliography that addresses the mitochondrial dysfunction and mitochondrial mechanisms implicated in ND and will discuss a relevant question in the field: is mitochondrial dysfunction a cause or consequence for these diseases?

Keywords: Neurodegenerative disease. Mitochondrial dysfunction. Alzheimer disease. Parkinson disease. Huntington disease.

Relevancia de las alteraciones mitocondriales en las enfermedades neurodegenerativas, una actualización y discusión de la evidencia

Resumen

Las enfermedades neurodegenerativas (EN) son, indudablemente, parte de los problemas de salud más importantes a nivel mundial. La pérdida de la independencia y disminución de la calidad de vida son características de estos pacientes que se traducen en una carga económica tanto para los familiares como para los servicios de salud. Aunque se han culpado a infinidad de factores o alteraciones metabólicas de ser los causantes, existe un defecto en común en casi toda las EN, la disfunción mitocondrial. La mitocondria es el principal proveedor de energía para la célula; por lo tanto, al alterar su función se verá afectada también la función celular en relación a la demanda de energía. Algunos defectos en los mecanismos mitocondriales como son la síntesis de ATP por la cadena respiratoria, la dinámica mitocondrial, la regulación de apoptosis, el estrés oxidativo, etc., se han descrito como parte de las características patológicas de enfermedades como Alzheimer, Parkinson, Huntington y Esclerosis Lateral Amiotrófica. En esta revisión describiremos brevemente las diferentes funciones mitocondriales en la vida de la célula, antes de analizar bibliografía recientemente publicada que aborda la disfunción y los

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mecanismos mitocondriales implicados en las EN y discutiremos una cuestión relevante en este campo: ¿Es la disfunción mitocondrial la causa o consecuencia de estas enfermedades?

Palabras clave: Enfermedad neurodegenerativa. Disfunción mitocondrial. Enfermedad de Alzheimer. Enfermedad de Parkinson. Enfermedad de Huntington.

Introduction

Neurodegenerative diseases (ND) are a set of central nervous system conditions whose main characteristic is the appearance of progressive damage that affects cognitive and motor functions. These diseases are usually of sudden onset, and there are no specific treatments to reverse or stop their progression; therefore, the patient's fate is death¹.

There are four NDs with the highest prevalence worldwide: Alzheimer's disease (AD), in the first place, is the leading dementia affecting 15/1000 people; Huntington's disease is a motor disease that afflicts 12/100000 people; and Parkinson's disease (PD) occurs in 5 out of 100000; whereas Amyotrophic Lateral Sclerosis (ALS) prevalence is 1.75-3/100000^{2,3}.

These diseases burden health systems worldwide because they are disabling and significantly deteriorate people's life quality and expectancy. In addition, there is a negative impact on the family life of affected people related to the high costs of the necessary care and treatment.

Although there are numerous theories about the origin of these ND, there is a lack of precision in pointing out the causes of these diseases, which results in the absence of etiological treatments; for that reason, therapies are usually only palliative⁴. A probable cause is the alteration in mitochondrial function or mitochondrial dysfunction, which is widely studied.

Mitochondria play fundamental roles in the central nervous system, that is, as a supplier of energy that cells need to fulfill their functions; therefore, the organelle's function must be kept in optimal condition because they are the cellular site for cellular ATP synthesis. Other main mitochondria functions are the regulation of intracellular calcium concentrations, functioning as transitory calcium stores and as a regulator and amplifier for intrinsic apoptosis, being a center where different intracellular routes converge, and, in addition, mitochondria participate in the synthesis of some steroids and neurotransmitters⁵.

In recent years, several reports have described severe alterations in different mitochondrial functions associated with primary ND (Table 1); however, it is still unclear whether mitochondrial dysfunction is a cause or one consequence of other pathological mechanisms existing in the evolution of these diseases.

Roles of mitochondria in health and disease

Mitochondrial ATP is synthesized through a mechanism known as oxidative phosphorylation carried out in the inner membrane by a serial group of five protein complexes named Electron Transport Chain (ETC) (ETC, Fig. 1). The ETC generates an electrochemical gradient by pumping protons from the mitochondrial matrix to the intermembrane space, using a flow of electrons between complexes I, II, III, and IV as an energy source. Finally, electrons are used to reduce oxygen to water. In contrast, the force generated by the proton gradient is used by ATP synthase to convert ADP and inorganic phosphate to ATP (the proton-motive force)⁶.

On the other hand, the mitochondria are the organelle where more free radicals are produced. In the processes of oxidative phosphorylation, oxygen is reduced to water by accepting two electrons. Still, this reduction can be incomplete and generate the radical superoxide in mitochondrial Complex I and IV of the ETC as an undesirable product of the ATP synthesis (Fig. 1). Under normal conditions, free radicals are produced in small amounts that either comply with physiological functions or are counteracted by an antioxidant system conformed by both enzymatic (superoxide dismutase, glutathione peroxidase, and catalase), and non-enzymatic compounds, such as ascorbic acid or Vitamin E^{7,8}.

Under pathological conditions, damage to its components or overload in the ETC may favor the overproduction of reactive oxygen species (ROS) or free radicals. In general, up to 2% of oxygen consumed by the ETC is partially reduced to superoxide but may increase significantly, forming another ROS like oxygen peroxide (Fig. 2). In the development and evolution of main ND, environments of high oxidative stress are generated⁹.

Mitochondria, contrasting with other organelles, cannot be generated *de novo*; therefore, they must be renewed from pre-existing mitochondria. This process, called mitochondrial dynamics, consists of two mechanisms: In mitochondrial fusion, two mitochondria come together to form one, to exchange their content and

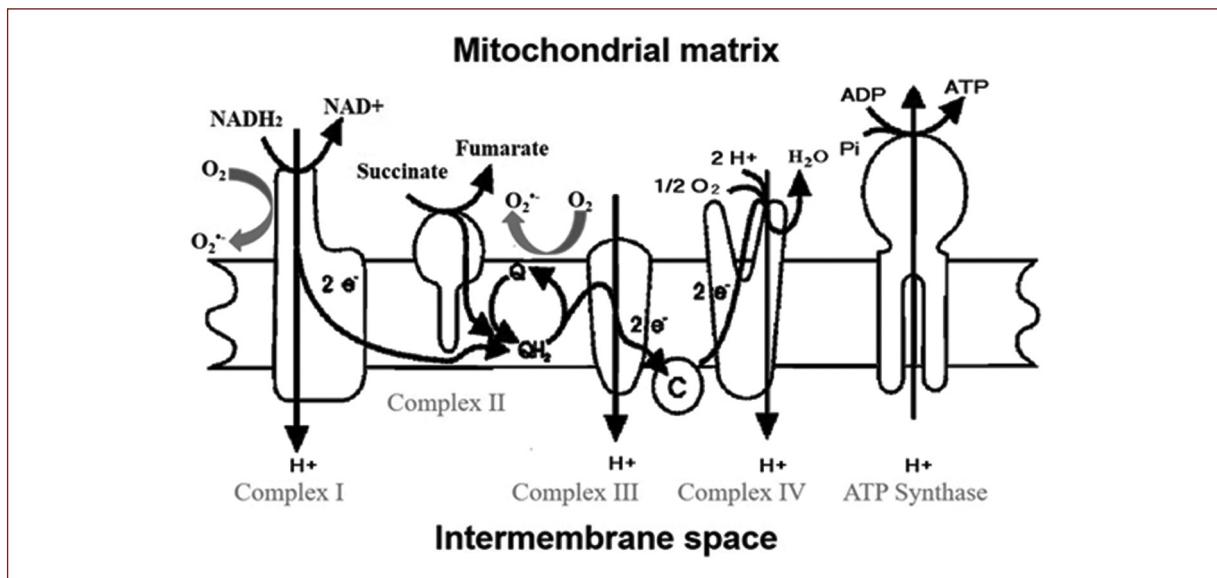


Figure 1. Schematic representation of the electrons flow through the mitochondrial electron transport chain, the translocation of protons by complexes I, III, and IV, and the synthesis of ATP by ATP synthase from ADP and phosphate; additionally, the figure shows the sites identified as the source of superoxide radicals: Complex I and Q-cycle. It was modified from Martinez-Abundis et al. 2005.

Table 1. Main mitochondrial alterations associated to clinical manifestations in patients with neurodegenerative diseases

Pathology	Clinical manifestation	Impaired structures	Mitochondrial disorder	References
Alzheimer	<ul style="list-style-type: none"> – Episodic and spatial memory loss – Learning difficulty – Language loss 	– Hippocampus	<ul style="list-style-type: none"> – Altered mitochondrial dynamics – Oxidative stress – Impaired apoptosis – Calcium imbalance 	Manczak <i>et al.</i> 2018 Reddy <i>et al.</i> 2018 Erickson <i>et al.</i> 2012
Parkinson	<ul style="list-style-type: none"> – Tremors – Parkinsonian gait – Hypogenesis – Dementia 	<ul style="list-style-type: none"> – Dopaminergic system – Locus niger 	<ul style="list-style-type: none"> – Altered mitochondrial dynamics – Oxidative stress – Impaired apoptosis 	Borsche <i>et al.</i> 2021 Rao <i>et al.</i> 2014 Lin and Beal, 2006
Huntington	<ul style="list-style-type: none"> – Motor deficit – Lack of emotion recognition – Lower processing speed – Visuospatial problems 	<ul style="list-style-type: none"> – Cerebral cortex – Hippocampus – Hypothalamus – Striatum – Putamen 	<ul style="list-style-type: none"> – Altered mitochondrial dynamics – Oxidative stress – Impaired apoptosis 	Naia <i>et al.</i> 2016 Costa <i>et al.</i> 2010 Benchoua <i>et al.</i> 2006
Lateral amyotrophic sclerosis	<ul style="list-style-type: none"> – Progressive motor deficit – Dementia in 5-15% of cases 	<ul style="list-style-type: none"> – Brainstem – Spinal cord 	<ul style="list-style-type: none"> – Oxidative stress – Impaired apoptosis 	D' Amico <i>et al.</i> 2013 Simpson <i>et al.</i> 2004 Wiedemann <i>et al.</i> 2002

thereby alleviate defects such as genetic mutations or functional damage in proteins resulting from the free radicals production¹⁰. The second process is fission when one mitochondrion divides in a controlled manner to generate two smaller organelles. Fission is necessary for generating a higher mitochondrial population

and may respond to an increased necessity of energy, or like fusion; it represents a way to deal with damaged mitochondria since smaller defective mitochondria may be eliminated by mitophagy. Mitochondrial dynamics are vital for neurons since the energy demand to carry out their functions is very high. These organelles'

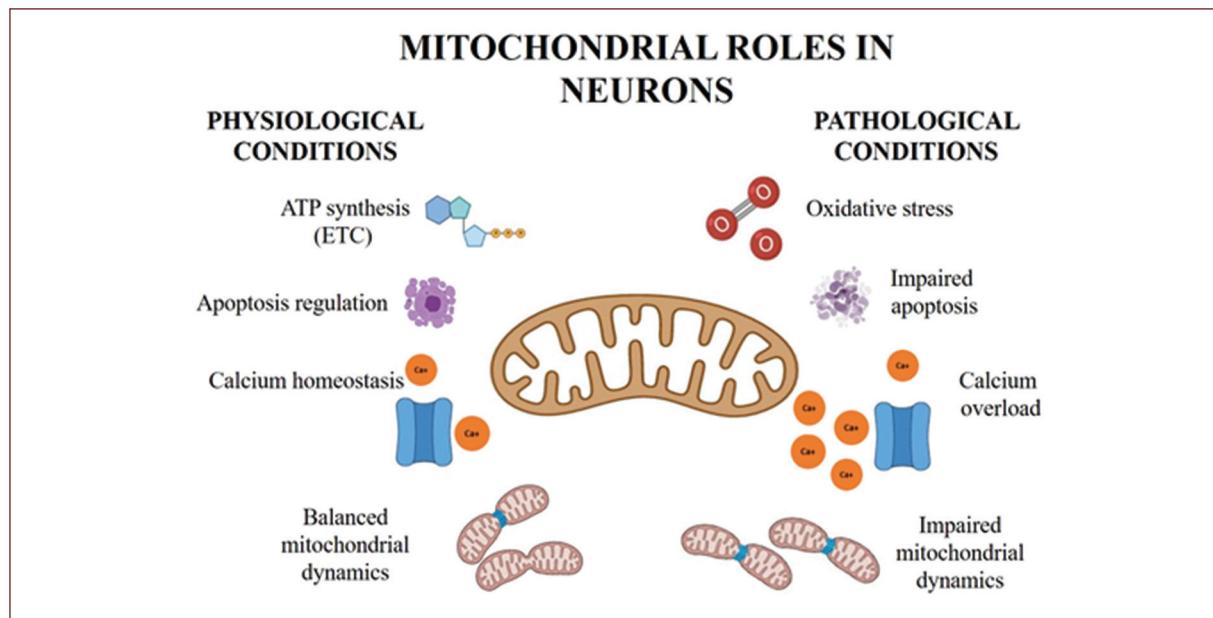


Figure 2. Schema shows the functions and events that occur in the mitochondria. On the left are the physiological processes in healthy neurons and on the right are the conditions in different pathological states associated with neurodegenerative diseases.

ETC: Electron Transport Chain.

cellular distribution impacts neuronal function, so even a tiny imbalance could be catastrophic for these cells.

Mitochondria regulate the intrinsic pathway of apoptosis, serving as a reservoir for some pro-apoptotic factors such as cytochrome c, which, once released to the cytosol, binds to the adapter protein Apaf 1 and procaspase 9 to assemble the apoptosome. This complex' function favors the caspase 9 self-activation and amplifies the apoptotic signaling to cell death¹¹. The extrinsic pathway, not dependent on mitochondria, begins with the activation of death receptors, including TNF type 1 and Fas, by external stimuli and ends with the activation of effector caspases¹². The intrinsic and extrinsic pathways may converge because caspase 8 activates Bid, a pro-apoptotic protein that further will translocate from the cytosol to the outer membrane of the mitochondria, increasing its permeability and allowing the release of cytochrome C¹³. Intrinsic apoptosis is tightly regulated through different mechanisms, for example, the Bcl-2 family of proteins (Bcl from B-cell Lymphoma) integrated by both pro- and anti-apoptotic members. Pro-apoptotic proteins such as Bad, Bid, and Bax promote the permeabilization of the outer mitochondrial membrane, whereas Bcl-2, Bcl-XL, among others, counteract these effects by acting as anti-apoptotic factors.

The opening of the mitochondrial permeability transition pore (mPTP), an unspecific transmembrane channel in the inner membrane that, once opens, allows the crossing of solutes, is another possible route for activating the intrinsic pathway of apoptosis. The mPTP is a channel whose structural identity is still under discussion; however, a hypothesis suggests it is integrated at least by three proteins: the constitutive outer membrane voltage-dependent anion channel, the inner membrane adenine nucleotide translocator and the isomerase cyclophilin D, located in the mitochondrial matrix. This pore is formed to regulate the mitochondrial excess of calcium. Still, some stimuli, such as the increase in ROS or a calcium overload, induce a more extended opening, causing mitochondrial swelling, a massive entrance of water, and the leakage of cytochrome c to the cytosol¹⁴.

Intracellular calcium levels play a fundamental role in neurons' functions, but high concentrations may disturb the bioenergetics and functionality of the mitochondria. The largest intracellular calcium reservoir is the endoplasmic reticulum; however, the mitochondria may contain it temporarily when a massive release to the cytosol. If the calcium overload is persistent, a collapse in the membrane potential, ATP depletion, and the generation of ROS will promote the activation of cell death¹⁵.

The proper function of mitochondria depends on two crucial processes: Biogenesis and mitophagy. The first comprises the formation and growth of new mitochondria from pre-existing ones, the mechanism described previously as mitochondrial dynamics. The whole process includes the replication of mitochondrial deoxyribonucleic acid (DNA), the synthesis of membranes' components, and the synthesis and importation of proteins encoded by both the mitochondrial and nuclear genomes. For the successful occurrence of these processes, tight coordination between the processing of both genomes (nuclear DNA codifies for most of the mitochondrial proteins, whereas mitochondrial DNA only codifies for a small number) is required.

Mitochondrial biogenesis is regulated mainly by Peroxisome proliferator-activated receptor gamma 1-alpha coactivator (PGC-1 α), among the nuclear respiratory cofactors 1 and 2 as well as receptors activated by peroxisome proliferators gamma¹⁶. On the other hand, mitophagy is the specific process for eliminating damaged mitochondria, being the only way to remove these organelles. The whole process is regulated mainly by two proteins, Protein Kinase 1 and Parkin, which first accumulate in the membrane of damaged mitochondria to promote their separation from the mitochondrial network, subsequent ubiquitination, and finally, their degradation¹⁷.

Alzheimer

Alois Alzheimer first described AD. It is one of the most relevant ND and the most frequent form of dementia; additionally, it is an age-specific disease mainly affecting people over 60 years¹⁸.

The gradual, progressive, and irreversible loss of cognitive abilities, such as spatial memory, working memory, and motor coordination, characterize AD. Although its origin is still unknown, the main pathophysiological characteristics of the disease are well identified: (1) the hyperphosphorylation of the TAU protein, a cytoskeleton stabilizer, induces its dissociation and tends to form aggregates called neurofibrillary tangles, which alter entirely the cellular structure, inducing its death; (2) the β -amyloid peptide is over-produced and tends to form neurotoxic aggregates called amyloid plaques, which alter the cellular structure and function. These changes usually start in the hippocampus; however, in advanced stages of AD, they may extend to the cerebral cortex¹⁹.

Regarding mitochondrial functions, the interaction between the β -amyloid peptide and its protein

precursor with mitochondria was described within the molecular alterations of AD, altering its normal functioning and making this a preponderant damaging event in neurodegeneration²⁰. The mitochondrial fission-associated protein Drp-1 is activated by nitrosylation in the hippocampus and cerebral cortex of genetically modified mouse models whose overexpression generates its accumulation. The expression of Fis-1, another fission-associated protein, is also increased. These changes also explain another pathological finding, the increased number of smaller mitochondria. In addition, the down-regulation of fusion proteins OPA 1 and mitofusin 1 and 2 was observed, rendering a lower rate of mitochondrial fusion and an imbalance toward fission. As fission is a vital process for the recycling of mitochondrial components, its stimulation can be interpreted as an indicator of the poor health of these organelles²¹ and the fact that increased fission is associated with the accidental release of cytochrome C and the activation of apoptosis.

In mouse hippocampal neurons treated with β -amyloid peptide, considered an *in vitro* model to study the pathogenesis related to the development of AD, mitochondrial fission was upregulated, and fusion downregulated in addition to alterations in both biogenesis and mitophagy. In addition, oxidative stress increases considerably due to the treatment²².

According to the previous reports, once in the cytosol, the β -amyloid peptide is internalized into the mitochondria through inner and outer membrane-located translocases²³, which may interfere with the importation of nuclear-encoded ETC subunits, affecting assembly or function of the mitochondrial complex. There is experimental evidence of impaired functioning of complexes I (NADH dehydrogenase), III (Cytochrome C Reductase), and IV (Cytochrome C Oxidase) as a result of β -amyloid peptide interaction. This effect modifies the oxidative phosphorylation (electron flow, the proton gradient, and mitochondrial potential), which finally will affect the synthesis of ATP by complex V (ATP synthase)²⁴ and increase the formation of ROS as sub-products (Fig. 2).

The triggering of oxidative stress by β -amyloid peptide has different consequences on the central nervous system cells; for example, it increases lipid peroxidation, affecting mainly the polyunsaturated fatty acids, constituents of biological membranes, which turned into loss of membranes fluidity, modification of the membrane potential and increased permeability. Proteins undergo oxidative damage, such as carbonylation and nitrosylation,

which modify their structure and compromise their functionality. Increased oxidative stress may also induce mitochondrial and nuclear DNA mutations, affecting the proteins' expression and function²⁵.

The tight regulation of calcium concentrations is essential for the properly functioning of the central nervous system. In this sense, the previous reports indicate that calcium homeostasis is altered in AD, probably because mitochondrial dysfunction decreases its capacity to absorb and retain calcium, specifically in the case of mitochondria located at the synaptic button. These disturbances in calcium management produce defects in the release of neurotransmitter-carrying vesicles. In addition, the endoplasmic reticulum releases stored calcium, increasing its cytosolic concentration and promoting the opening of pores in the mitochondrial membrane that allow the releasing of pro-apoptotic factors, including cytochrome C, which finally activate the intrinsic pathway of apoptosis²⁶. The decreased size of structures such as the hippocampus and cerebral cortex that characterizes AD is associated with increased apoptotic cell death, which is recognized as the leading cause of the decline in cognitive abilities that characterize this disease²⁷.

There are additional mechanisms reported for mitochondrial damage; for example, aging is associated with structural and functional changes, including a decrease in the number of inner membrane cristae, the dissociation of ATP synthetase dimers, and the accumulation of mutations in mitochondrial DNA, which culminates in metabolic alterations, accompanied by an environment of high oxidative stress and apoptosis which finally is potentiated by the characteristic accumulation of β -amyloid.

Genetics could be a central pathological component contributing to the transition from mitochondrial failures to dysfunction. The mitochondrial DNA is highly susceptible to mutations induced by the oxidative stress generated by the organelle, which, added to the lack of histone protection, may accentuate the failures in energy metabolism since the mitochondrial genome codifies for numerous subunits of protein complexes of the respiratory chain.

Similarly, lifestyle and environment may increase the risk of developing AD. Exposure to toxins such as pesticides, xenobiotics, and heavy metals induces neurotoxicity and mitochondrial dysfunction, which causes symptoms similar to those of Alzheimer's disease. On the other hand, the consumption of hypercaloric diets is associated with a deficit in mitochondrial functioning due to an increased generation of oxidative stress²⁸.

The mitochondrial defects mentioned above modify the energy metabolism; therefore, positron emission tomography and fluorodeoxyglucose (FDG-PET) can be used for the diagnosis of the disease because the detection of a lower uptake of cerebral glucose is possible with this technique and may be related to cognitive symptoms in patients with the presence of Alzheimer disease²⁹.

PD

PD was described by James Parkinson in 1817 and called palsy agitans². It is a progressive neurological disorder that courses with motor symptoms such as bradykinesia (slowness of movement), stiffness, or involuntary resistance to movement, besides tremors at rest and postural instability due to the difficulty in maintaining or changing postures while walking or walking stand. Non-motor and psychiatric symptoms may also occur as loss of smell, difficulty sleeping, REM sleep disorders, constipation, urinary frequency, erectile dysfunction, orthostatic hypotension, and changes in blood pressure. In addition, symptoms such as anxiety, depression, psychosis, apathy, and dementia are added³⁰.

The neuropathology of PD involves mainly the deregulation of dopaminergic neurotransmission, degeneration of nerve fibers, and neuronal death due to α -synuclein deposits forming structures known as Lewy bodies. The affected structures in the central nervous system are the cerebral cortex, the brain stem, the spinal cord, the hypothalamus, and the insula. In contrast, at the peripheral level, the enteric neural plexus and the vagus nerve are affected³¹.

According to reports, the mitochondrial damage in PD is extensive. The protein α -synuclein accumulates inside the mitochondria of people's brains, interfering with the ETC by decreasing the activity of complex I (NADH dehydrogenated) and simultaneously increasing oxidative stress by overproduction of ROS³².

Results from experimental models indicate that blocking complex I of the ETC induces dysfunction in dopaminergic neurotransmission³³; the main transmission route affected in Parkinson's disease is the substantia nigra, which initially decreases the complex I activity. In addition, reports indicate that mitochondrial complex I subunits are oxidized, and activity is reduced in multiple tissues from individuals with sporadic PD, probably associated with incorrect assembly and anchoring of complex I to the inner mitochondrial membrane³⁴. These effects are associated with an increase

in the mitochondrial permeability transition, which raises the generation of ROS and, therefore, a state of oxidative stress in the central nervous system³⁵.

Mitochondrial dysfunction may also result from defects in biogenesis, as suggested by the analysis of the substantia nigra samples obtained from autopsies of patients with PD, where the coactivator of transcription factors PGC-1 α expression was downregulated³⁶; such a result correlated with the increased expression and oligomerization of α -synuclein³⁷. On the other hand, an increased expression of Pink and Park, the main proteins involved in mitophagy regulation, suggests this process is also affected⁹.

There are rare, autosomal, and dominant forms of the disease that include mutations in the PINK1 (PTEN-induced kinase 1) and PARKIN (ubiquitin ligase) genes, which were described as causing a pathology very similar to sporadic PD; however, they could be considered more a type of parkinsonism than the true disease whose primary etiological agent is accumulations of α -synuclein³⁸.

These genes control the elimination of defective mitochondria, adjusting the mitochondrial network and thus maintaining the homeostasis of energy metabolism. PINK1 regulates the translocation of PARKIN in damaged mitochondria and promotes its elimination through a type of selective autophagy (mitophagy); as these genes are mutated and the consequent defective production of these proteins, as well as the lack of expression of the same, they interrupt the signaling for the initiation of mitophagy, therefore, there is an accumulation of damaged mitochondria, and accumulation of more failures in energy metabolism³⁹.

Huntington disease

It is an autosomal dominant disease, described first by George Huntington in 1872, who discovered its hereditary nature. Huntington's disease (HD) is a motor disorder such as chorea (involuntary and irregular movements of extremities) and loss of coordination, with the appearance of psychiatric symptoms such as depression, psychosis, and obsessive-compulsive disorder. The brain structures damaged in this disease are the caudate nucleus and the putamen; both are part of the striatum. In addition, there is a loss of spinous efferent neurons and a thinning of the cerebral cortex, which occurs at the early stages of the disease and may explain its heterogeneity⁴⁰.

The HD-associated disturbances result from mutations in the gene that codes for Huntington. This 350 kDa

protein contains uninterrupted repeats of CAG triplets in its first exon. While the normal allele includes a maximum of 35 repetitions, the mutant allele contains 36 or more. Significant findings are that only a small number of patients with 36-41 repeats have symptoms and that at a higher number of repetitions, the age for the onset of symptoms is lower⁴¹.

Postmortem studies carried out either in the brains of patients with HD or in experimental models showed a dramatic decrease in the activity of mitochondrial complexes II, III, and IV in both the caudate nucleus and putamen^{42,43} which is associated with low ATP levels, increased oxidative stress and cell dysfunction⁴⁴. These disturbances may result from a decrease in glucose metabolism since alterations in the function of the enzyme glyceraldehyde 3-phosphate dehydrogenase were detected (GAPDH)⁴⁵.

On the other hand, mitochondria's morphology is abnormal due to an imbalance between fusion and fission, assessed as an increased expression in the fission-related proteins Drp-1 and Fis-1, besides a decrease in the fusion-related proteins, mitofusins, and OPA-1 (Fig. 2). As described above, this modification in either the brains of patients with the disease or in experimental models leads to excessive mitochondria fragmentation⁴⁶.

ALS

It is a progressive motor disease described by the French physician Jean-Martin Charcot in 1869. The main feature of this disease is the degeneration of both the upper motor neurons that connects the cortex with the brainstem and spinal cord, as well as the lower motor neurons that link the brainstem and spinal cord with the muscle; that is why the symptoms are usually motor and extra-motor⁴⁷. Signs that progress over weeks or months include dysarthria, slurred speech, spasticity or muscle stiffness, dysphagia or difficulty swallowing, and muscle weakness. Unlike other motor diseases, such as PD or Huntington's chorea, psychiatric symptoms do not manifest in ALS. Patients suffering from this disease and their families may improve their quality of life with palliative and supportive therapies.

The pathophysiology of ALS is partially unknown; however, aggregates of a protein called TDP-43 were identified in people with this disease. This protein is encoded in the TARDBP gene, and the formation of aggregates is associated with the misfolding induced by genetic mutations⁴⁸. Like the other ND, mitochondria

may be one of the most affected organelles since ATP generation is decreased, possibly due to reduced activity of complexes I, II, III, and IV^{49,50}. In addition, there is an increase in the production of ROS, oxidative stress⁵¹, and, finally, a high rate of lipid peroxidation⁵².

Alteration in genes involved in mitochondrial function and homeostasis have been described in patients and mouse models with the disease; for example, mutations in the antioxidant enzyme Superoxide dismutase 1 gene, which has cytosolic and mitochondrial isoforms, favors the formation of mitochondrial aggregates, inhibiting respiration⁵³. On the other hand, the gene that encodes the C9ORF72 protein suffers mutations in ALS, which trigger the formation of toxic mitochondrial aggregates, and increases the mitochondrial membrane potential along with the formation of ROS. In addition, this protein participates in the assembly of Complex I and interacts with the ATP5A subunit of Complex V; hence, its mutations may translate into a dysfunctional Complex I and a decrease in ATP production, respectively.

It has been reported that the gene that encodes the RNA- binding protein FUS (FUS) is altered at the early stages of ALS. This protein is responsible for directing the mRNA encoding the respiratory chain proteins, which hinders their expression with consequences such as disruption of the mitochondrial network, decreased oxygen consumption, and increased ROS production.

Mutations in the gene that encodes the Vesicle-associated membrane protein B that participates in the transfer of lipids, as well as calcium ions, have diverse effects on mitochondrial function as a lower importation of calcium from the endoplasmic reticulum to mitochondria, reduction in the activity of the respiratory chain and, it has also been associated with defective autophagy.

Similarly, mutations in other genes responsible for mitochondrial quality control and mitophagy, such as Valolin-containing protein, Optineurin, and TANK-binding kinase 1, which hinders proper mitochondrial transport and recycling, were described. Mutations in the SIGMAR1 gene that encodes the Sigma 1 opioid receptor induce a rupture of mitochondrial membranes, resulting in a loss of membrane potential and a decreased ATP production.

Finally, the gene for the Kinesin family member 5, a protein that participates in the transport of organelles, including mitochondria, is affected, resulting in its incorrect distribution through the neuron⁵³.

Conclusion

Mitochondrial dysfunction is a common characteristic in the main ND, which is unsurprising, considering its relevance for the ATP supply to cells. The energy supply to neurons is compromised under pathophysiological environments, with a collapse in ATP production and an increase in ROS generation; both are commonly found and, even more, may be considered markers for the pathophysiology of ND. In addition, some mitochondrial mechanisms, such as fission and fusion, biogenesis, and mitophagy, which participate in the recycling and maintenance of the organelle are often affected. Neurons' functionality depends on a strictly controlled environment; these changes can ultimately lead cells to apoptotic death and neurodegeneration (Fig. 2). Nowadays, the evidence of mitochondrial alterations' participation in ND is abundant; the evidence also indicates that preventing mitochondrial dysfunction may diminish or stop the progression of neurological damage, placing mitochondrial dysfunction as an essential part of the disease process over a single consequence.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

- Katsuno M, Sahashi K, Iguchi Y, Hashizume A. Preclinical progression of neurodegenerative diseases. *Nagoya J Med Sci.* 2018;80:289-98.
- Simon DK, Tanner CM, Brundin P. Parkinson disease epidemiology, pathology, genetics, and pathophysiology. *Clin Geriatr Med.* 2020;36:1-12.
- Tabrizi SJ, Flower MD, Ross CA, Wild EJ. Huntington disease: new insights into molecular pathogenesis and therapeutic opportunities. *Nat Rev Neurol.* 2020;16:529-46.
- Nissanka N, Moraes CT. Mitochondrial DNA damage and reactive oxygen species in neurodegenerative disease. *FEBS Lett.* 2018;592:728-42.
- Vanhauwaert R, Bharat V, Wang X. Surveillance and transportation of mitochondria in neurons. *Curr Opin Neurobiol.* 2019;57:87-93.
- Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. *Cell.* 2012;148:1145-59.
- Zinovkin RA, Zamyatin AA. Mitochondria-targeted drugs. *Curr Mol Pharmacol.* 2019;12: 202-14.
- Njus D, Kelley PM, Tu YJ, Schlegel HB. Ascorbic acid: the chemistry underlying its antioxidant properties. *Free Radic Biol Med.* 2020; 159:37-43.
- Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature.* 2006;443:787-95.
- Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. *Essays Biochem.* 2018;62:341-60.
- Estaquier J, Vallette F, Vaysseire J, Mignotte B. The mitochondrial pathways of apoptosis. *Adv Exp Med Biol.* 2012;942:157-83.
- Elmore S. Apoptosis: a review of programmed cell death. *Toxicol Pathol.* 2007;35:495-516.
- Sekar G, Ojoawo A, Moldoveanu T. Protein-protein and protein-lipid interactions of pore-forming BCL-2 family proteins in apoptosis initiation. *Biochem Soc Trans.* 2022;50:1091-103.
- Bauer TM, Murphy E. Role of mitochondrial calcium and the permeability transition pore in regulating cell death. *Circ Res.* 2020;126:280-93.
- Rossi A, Pizzo P, Filadi R. Calcium, mitochondria and cell metabolism: a functional triangle in bioenergetics. *Biochim Biophys Acta Mol Cell Res.* 2019;1866:1068-78.
- Li PA, Hou X, Hao S. Mitochondrial biogenesis in neurodegeneration. *J Neurosci Res.* 2017;95:2025-9.
- Ashrafi G, Schwarz TL. The pathways of mitophagy for quality control and clearance of mitochondria. *Cell Death Differ.* 2013;20:31-42.
- Villain N, Dubois B. Alzheimer's disease including focal presentations. *Semin Neurol.* 2019;39:213-26.
- Soria-Lopez JA, Gonzalez HM, Léger GC. Alzheimer's disease. *Handb Clin Neurol.* 2019;167:231-55.
- Pavlov PF, Wiegner B, Sakai J, Frykman S, Behbahani H, Winblad B, et al. Mitochondrial γ -secretase participates in the metabolism of mitochondrial-associated amyloid precursor protein. *FASEB J.* 2011;25:78-88.
- Manczak M, Kandimalla R, Yin X, Reddy PH. Hippocampal mutant APP and amyloid beta-induced cognitive decline, dendrite spine loss, defective autophagy, mitophagy and mitochondrial abnormalities in a mouse model of Alzheimer's disease. *Hum Mol Genet.* 2018;27:1332-42.
- Reddy PH, Yin X, Manczak M, Kumar S, Pradeepkiran JA, Vijayan M, et al. Mutant APP and amyloid beta-induced defective autophagy, mitophagy, mitochondrial structural and functional changes and synaptic damage in hippocampal neurons from Alzheimer's disease. *Hum Mol Genet.* 2018;27:2502-16.
- Anandatheerthavarada HK, Biswas G, Robin MA, Avadhani NG. Mitochondrial targeting and a novel transmembrane arrest of Alzheimer's amyloid precursor protein impairs mitochondrial function in neuronal cells. *J Cell Biol.* 2003;161:41-54.
- Eckert A, Schulz KL, Rhein V, Götz J. Convergence of amyloid-beta and tau pathologies on mitochondria *in vivo*. *Mol Neurobiol.* 2010;41:107-14.
- Gaschler MM, Stockwell BR. Lipid peroxidation in cell death. *Biochem Biophys Res Commun.* 2017;482:419-25.
- Cali T, Ottolini D, Brini M. Mitochondrial Ca(2+) and neurodegeneration. *Cell Calcium.* 2012;52:73-85.
- Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. *Arch Med Res.* 2012;43:615-21.
- Sharma C, Kim S, Nam Y, Jung UJ, Kim SR. Mitochondrial dysfunction as a driver of cognitive impairment in Alzheimer's disease. *Int J Mol Sci.* 2021;22:4850.
- Perez Ortiz JM, Swerdlow RH. Mitochondrial dysfunction in Alzheimer's disease: role in pathogenesis and novel therapeutic opportunities. *Br J Pharmacol.* 2019;176:3489-507.
- Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna).* 2017;124:901-5.
- Chen Z, Li G, Liu J. Autonomic dysfunction in Parkinson's disease: implications for pathophysiology, diagnosis, and treatment. *Neurobiol Dis.* 2020;134:104700.
- Borsche M, Pereira SL, Klein C, Grünewald A. Mitochondria and Parkinson's disease: clinical, molecular, and translational aspects. *J Parkinsons Dis.* 2021;11:45-60.
- Perier C, Bové J, Dehay B, Jackson-Lewis V, Rabinovitch PS, Przedborski S, Vila M. Apoptosis-inducing factor deficiency sensitizes dopaminergic neurons to Parkinsonian neurotoxins. *Ann Neurol.* 2010;68:184-92.
- Keeney PM, Xie J, Capaldi RA, Bennett JP Jr. Parkinson's disease brain mitochondrial complex I has oxidatively damaged subunits and is functionally impaired and misassembled. *J Neurosci.* 2006;26:5256-64.
- Rao VK, Carlson EA, Yan SS. Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. *Biochim Biophys Acta.* 2014;1842:1267-72.
- Zheng B, Liao Z, Locascio JJ, Lesniak KA, Roderick SS, Watt ML, et al. Global PD Gene Expression (GPEX) Consortium. PGC-1 α , a potential therapeutic target for early intervention in Parkinson's disease. *Sci Transl Med.* 2010;2:52ra73.
- Eschbach J, von Einem B, Müller K, Bayer H, Scheffold A, Morrison BE, et al. Mutual exacerbation of peroxisome proliferator-activated receptor γ coactivator 1 α deregulation and α -synuclein oligomerization. *Ann Neurol.* 2015;77:15-32.
- Rocha EM, De Miranda B, Sanders LH. Alpha-synuclein: pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. *Neurobiol Dis.* 2018;109:249-57.
- Malpartida AB, Williamson M, Narendra DP, Wade-Martins R, Ryan BJ. Mitochondrial Dysfunction and mitophagy in Parkinson's disease: from mechanism to therapy. *Trends Biochem Sci.* 2021;46:329-43.
- Jimenez-Sanchez M, Licitra F, Underwood BR, Rubinstein DC. Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. *Cold Spring Harb Perspect Med.* 2017;7:a024240.
- Wyant KJ, Ridder AJ, Dayalu P. Huntington's disease-update on treatments. *Curr Neurol Neurosci Rep.* 2017;17:33.
- Maksimović ID, Jovanović MD, Colić M, Mihajlović R, Mićić D, Šešlaković V, et al. Oxidative damage and metabolic dysfunction in experimental Huntington's disease: selective vulnerability of the striatum and hippocampus. *Vojnosanit Pregl.* 2001;58:237-42.
- Benchoua A, Trioulier Y, Zala D, Gaillard MC, Lefort N, Dufour N, et al. Involvement of mitochondrial complex II defects in neuronal death produced by N-terminus fragment of mutated huntingtin. *Mol Biol Cell.* 2006;17:1652-63.
- Naia L, Ribeiro M, Rodrigues J, Duarte AI, Lopes C, Rosenstock TR, et al. Insulin and IGF-1 regularize energy metabolites in neural cells expressing full-length mutant huntingtin. *Neuropeptides.* 2016;58:73-81.
- Mazziotta JC, Phelps ME, Pahl JJ, Huang SC, Baxter LR, Riege WH, et al. Reduced cerebral glucose metabolism in asymptomatic subjects at risk for Huntington's disease. *N Engl J Med.* 1987;316:357-62.
- Costa V, Giacometti M, Hudec R, Lopreiato R, Ermak G, Lim D, Malorni W, et al. Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli. *EMBO Mol Med.* 2010;2:490-503.
- Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, et al. Amyotrophic lateral sclerosis. *Nat Rev Dis Primers.* 2017;3:17071.
- Prasad A, Bharathi V, Sivalingam V, Girdhar A, Patel BK. Molecular mechanisms of TDP-43 misfolding and pathology in amyotrophic lateral sclerosis. *Front Mol Neurosci.* 2019;12:25.
- Borthwick GM, Johnson MA, Ince PG, Shaw PJ, Turnbull DM. Mitochondrial enzyme activity in amyotrophic lateral sclerosis: implications for the role of mitochondria in neuronal cell death. *Ann Neurol.* 1999;46:787-90.
- Wiedemann FR, Manfredi G, Mawrin C, Beal MF, Schon EA. Mitochondrial DNA and respiratory chain function in spinal cords of ALS patients. *J Neurochem.* 2002;80:616-25.
- D'Amico E, Factor-Litvak P, Santella RM, Mitsumoto H. Clinical perspective on oxidative stress in sporadic amyotrophic lateral sclerosis. *Free Radic Biol Med.* 2013;65:509-27.
- Simpson EP, Henry YK, Henkel JS, Smith RG, Appel SH. Increased lipid peroxidation in sera of ALS patients: a potential biomarker of disease burden. *Neurology.* 2004;62:1758-65.
- Jankovic M, Novakovic I, Dawod PG, Dawod AG, Drinic A, Motaleb FI, et al. Current concepts on genetic aspects of mitochondrial dysfunction in amyotrophic lateral sclerosis. *Int J Mol Sci.* 2021;22:9832.