

Review

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Review

Alpha Synuclein Toxicity and Non-Motor Parkinson's

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Abstract: Parkinson's disease (PD) is a common multisystem neurodegenerative disorder affecting 1% of the population above 60 years. The main neuropathological features of PD are the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of alpha synuclein (aSyn)-rich Lewy bodies both manifesting with classical motor signs. aSyn has emerged as a key protein in PD pathology as it can spread through synaptic networks to reach several anatomical regions of the body contributing to the appearance of non-motor symptoms (NMS) considerate prevalent among individuals before PD diagnosis and persisting throughout the patient's life. NMS mainly include loss of taste and smell, constipation, psychiatric disorders, dementia, rapid eye movement (REM) sleep behavior impairment, urogenital dysfunction, and cardiovascular impairment. This review summarizes the more recent findings showing the impact of aSyn deposits on several prodromal NMS and emphasizes the importance of early detection of aSyn toxic species in biofluids and peripheral biopsies as prospective biomarkers in PD.

Keywords: alpha synuclein; Parkinson's disease; non-motor symptoms; early diagnosis

1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, second only to Alzheimer's disease, that refers to the group of α -synucleinopathies characterized by loss of the dopaminergic and monoaminergic neurons in the substantia nigra pars compacta (SNpc) and ventral tegmental area, as well as by the accumulation, aggregation and spread of α -Synuclein (α Syn) within neurons and non-neuronal cells including microglia, pericytes, astrocytes, and oligodendrocytes [1]. PD is the most common form of movement disorder clinically manifested by bradykinesia, dyskinesia, rest tremor, rigidity, slowness of movement, freezing, dizziness and postural instability as a result of the loss of 70-80% of the dopaminergic neurons in the substantia nigra *pars compacta* (SNpc) [2]. Aside from motor manifestations, PD impacts a plethora of non-motor symptoms (NMS) which may antedate the onset of movement disorders by several years [3,4]. They include smell-related alterations [5,6], dysfunction of the circadian rhythms [7], autonomic disorders such as orthostatic hypotension constipation, urinary difficulties, gastrointestinal disorders, anxiety, depression, and impairment or loss of sensory perception [4,8,9]. Non-motor manifestations have been recognized as significant contributors to the overall impact of the disease on the individual's quality of life [10–12].

According to Braak stage 1, early NMS such as smell disorders experienced by PD patients are caused by neuronal degeneration in the olfactory bulb and in anterior olfactory nucleus, while Braak stage 2 involves the lower brainstem i.e., raphe nucleus, locus coeruleus, pedunculopontine nucleus and thalamocortical system, which are associated with sleep disturbance, autonomic dysfunctions, visual hallucinations, and rapid eye movements [13].

Dysfunction of the medullary nuclei located in the brainstem, namely nucleus tractus solitarius, dorsal motor nucleus of the vagus, and nucleus ambiguus, regulate various involuntary functions including arterial blood pressure, heart rate, respiratory activity, and renal function. These conditions

are associated with orthostatic hypotension, cardiovascular abnormalities, and other autonomic disorders in PD [14]. The emergence of the classic motor symptoms of PD typically occurs at Braak stages 3 and 4. These clinical signs coincide with the involvement of key regions such as the SN_{pc} and other deep nuclei of the midbrain and the forebrain [15]. In the final stages Braak 5 and 6, Lewy bodies are found in the limbic structures and mature neocortex. At these stages, patients with PD can experience a variety of neuropsychiatric symptoms, including depression, cognitive impairment, and visual hallucinations [15]. The subthalamic nucleus plays a crucial role in PD. It receives inputs from sensorimotor, associative, and limbic brain regions which serve distinct functions within the basal ganglia circuitry. Specifically, pallidum-subthalamic projection is thought to underlie cognitive, emotional, and motivational NMS. This intricate organization underscores the diverse roles of the subthalamic nucleus in both motor and non-motor aspects of PD.

Several studies have reported effective role for the subthalamic nucleus deep brain stimulation (STN-DBS) on motor and NMS, although PD patients with longer disease duration had limited motor benefits from STN-DBS [16–19]. Case reports and data from a meta-analysis conducted on dozens of studies indicate that STN-DBS improve NMS and PD patient quality of life [20–23]. Due to the complexity of PD, a more comprehensive understanding of the underlying mechanisms beyond the scope of the Braak staging model is required. Certainly, the recognition of non-motor signs can contribute to early diagnosis of PD and help to adopt strategies aimed at improving the management of the disease [24]. In this review, we highlight recent advance in α Syn neurotoxicity that have contributed to our understanding of NMS onset and could aid in the development of future treatment strategies and/or early diagnosis.

2. α Syn Toxicity

From pathological point of view, NMS are the consequence of the formation of intracytoplasmic Lewy bodies and neurites rich in α Syn aggregates in nigral and extranigral areas.

α Syn is a small, 140 amino acid presynaptic acidic protein encoded by the SNCA gene whose main function seems to be the control of neurotransmitter release [25]. It is a vesicle-bound multimer consisting of three distinct regions: 1) the N-terminus (residues 1-60) crucial for its interaction with lipid membranes [26,27]; 2) the central hydrophobic region (residues 61-95) prone to aggregation named non-amyloid- β component (NAC region) [28] 3) the unstructured C-terminus (residues 96-140) highly negatively charged with Ca²⁺ binding and chaperone-like activity [29].

In the CNS, it exists in a soluble cytosolic fraction (for as much as 1% of the total protein) and in two membrane- and vesicle-binding forms: via C-terminal domain it interacts with vesicle-associated membrane protein 2 leading to the formation of vesicle clusters [30] and affecting vesicle docking as well as the inhibition of vesicle fusion, while via N-terminal region α Syn was found to bind membrane lipids. This membrane-binding pool seems to prevent the pathological aggregation [31–33]. Mutations in this domain are associated with PD pathology [34,35]. On the contrary, the cytosolic fraction is intrinsically disordered and behaves like a natively unfolded protein, contributing to the formation of aggregate species [36].

Different factors, such as genetic mutations [37], elevated levels of α Syn, mitochondrial dysfunction [38], oxidative stress (OS) [39], endoplasmic reticulum (ER) stress [40] dysregulation of synaptic vesicle recycling [41], and autophagy-lysosomal system [42], are well-known to concur to the α Syn misfolding, formation of β -sheet rich oligomers and fibrils in Lewy bodies or Lewy neurites accompanying NMS [43–46]. Studies also support the contribution of neuroinflammation in NMS [47–49], pointing to the essential components of the innate immune response such as the toll-like receptors (TLRs) [50–53]. In particular, pathogen associated molecular patterns and damage-associated molecular patterns (DAMPs) can prime and activate the TLRs creating a neuroinflammatory status which may culminate with neuronal death in specific brain areas [54]. Human studies suggest a role for TLR2 and TLR4 in the recognition of toxic species of α Syn as a DAMP which precede the α Syn aggregation [55,56]. Furthermore, polymorphisms in the SNCA gene are also well recognized factors concurring in the non-motor signs development [57]. NMS also are the consequence of the diffusion of the pathological species of α Syn. In fact, α Syn aggregates spread

between interconnected brain areas in a cell-to-cell and prion-like fashion which involve neurons and non-neuronal cells [58,59]. Transsynaptical transmission of α Syn may be triggered by the oligomeric α Syn-mediate microglia activation in the early phases of the disease [60] or by interactions between endogenous α Syn and mitochondria [61,62]. However, cells differentially mediate the uptake of the α Syn fibrils involving processes such as receptor-mediated endocytosis, extracellular vesicles and tunneling nanotubes. Fibrils can be sequestered and degraded into lysosomes or be trafficked into the cytosol via endocytic pathways, where they can interact with and recruit monomeric α Syn into mature pathological inclusions [63]. In addition, fibrils can be released by damaged or dead cells following mitochondrial dysfunction [38,51,64], disruption of redox balance [39], nitrosative stress [65], impaired autophagic flux [42], and prolonged ER stress [40]. Oligomeric α Syn may alter the voltage-gate receptors resulting in impairment of calcium efflux [66,67].

A schematic representation of the relation between α Syn toxic species and cellular dysfunctions is reported in Figure 1.

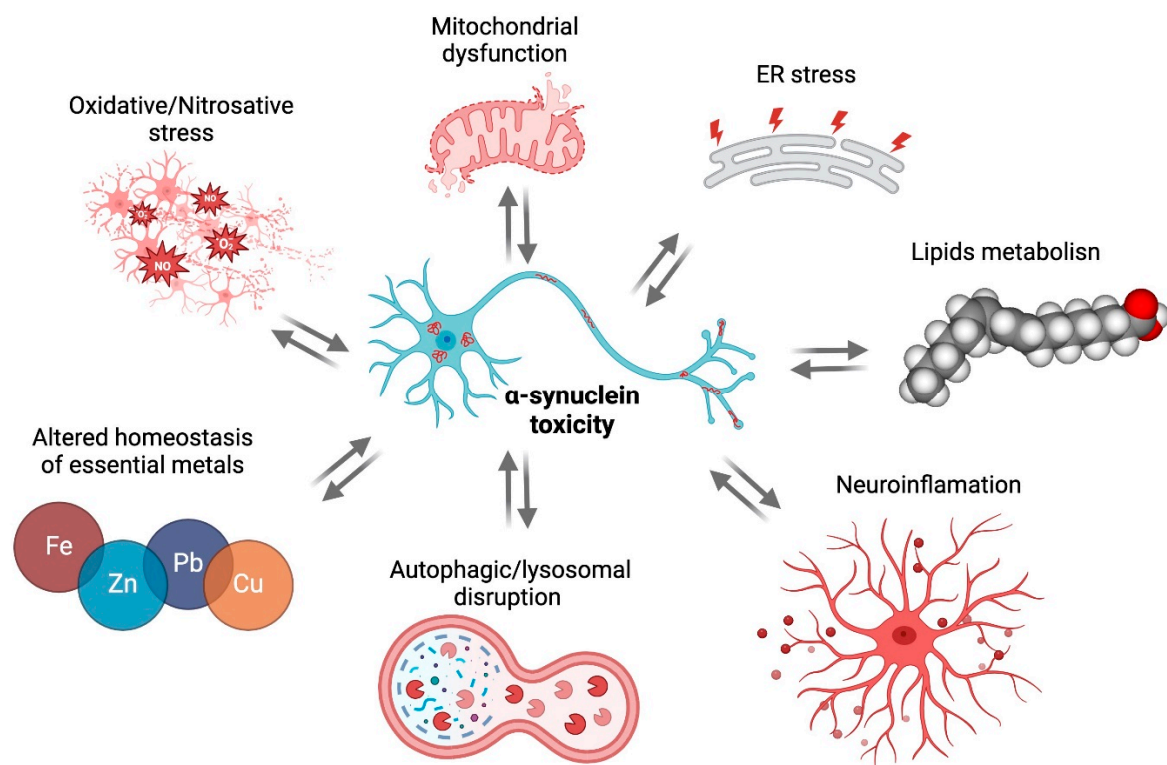


Figure 1. Bi-directional relation between α Syn toxic species and cellular dysfunctions. Different factors are well-known to concur to the generation of misfolded α Syn toxic species. On the other hand, abnormal levels or misfolded forms of α Syn impact on several aspects of neuronal function, thus contributing to the pathogenesis of PD. Created with Biorender.com.

2.1. Oxidative/Nitrosative Stress

A bidirectional relationship between oxidative/nitrosative stress and α Syn toxicity exists [68]. High levels of reactive oxidative species (ROS) within the neurons have been suggested to induce α Syn toxicity [69–71]. Excessive OS, cause peroxidation of the membrane lipids followed by the production of the highly toxic 4-hydroxy-2-nonenal. This compound induces the formation of beta sheets and toxic soluble oligomers of α Syn which are believed to promote neuronal damage [72,73]. Over, hydroxyl radical species can react with tyrosine residues on α Syn contributing to the formation of intramolecular oxidative covalent cross-linkage between two tyrosine residues known as the dityrosine bond [74]. Two opposing effects have been described for dityrosine: (i) formation and stabilization of α Syn insoluble fibrils or aggregates [75], and (ii) inhibition of α Syn fibrillation by dityrosine-modified monomer and dimers [74]. As aggregation proceeds, dityrosine formation shifts

from an aggregation-inhibiting to an aggregation-promoting element [76]. The higher-order assembly as well as increased stability of growing fibrils appear significantly to reduce their capacity to seed further aggregation because to the minor available surface area for serving as effective nucleation site and the conversion to less dynamic structures. Again, changes in hydrophobicity or charge distribution aside from changing the equilibrium between monomers, oligomers, and fibrils could influence the incorporation of additional monomers and aggregation kinetics [77].

Hypochlorite-oxidized cysteinyl-dopamine obtained by exposing cysteinyl-dopamine to hypochlorite is considered a potent redox cyclor able to accelerate OS and contribute to an excessive demand for autophagy and ultimately to cell death [78]. Additionally, post-translationally aberrant S-nitrosylation by reactive nitrogen species and nitric oxide in neurons is known to induce to aSyn misfolding and toxicity, axo-dendritic-, and dopamine dysfunction [79]. Moreover, Kumar et al. [80] showed that S-nitrosylation of the ubiquitin C-terminal hydrolase-1 provides a nucleation to the native aSyn accelerating the protein aggregation.

2.2. Mitochondrial Dysfunction

Mitochondrial dysfunction plays a central role in the pathogenesis of PD [81]. Several neurotoxins have been found to provoke high levels of ROS, complex I inhibition and neuronal damage [70]. Additionally, abnormal levels or misfolded forms of α Syn can disrupt the balance of mitochondrial fission and fusion and transport, leading to fragmentate or aggregate mitochondria, impairment of mitochondrial trafficking, electron transport chain, and calcium signaling [81,82]. α Syn can interact with complex I, resulting in decreased ATP production and increased ROS [83]. The selective autophagic degradation of damaged mitochondria can overwhelm the cellular proteostasis, leading to the accumulation of misfolded α Syn and mitochondrial dysfunction [84–86]. α Syn can trigger the opening of the mitochondrial permeability transition pore, causing mitochondrial swelling and loss of membrane potential [87] and can interact with other proteins involved in mitochondrial quality control, such as Parkin and PINK [88]. Dysregulation of these interactions can impair mitochondrial function and dynamics, contributing to the pathogenesis of PD.

2.3. ER Stress

The accumulation of newly synthesized or improperly folded proteins in the ER can saturate the folding machinery, leading to ER stress which promptly activates the unfolded protein response (UPR) aims to restore normal ER function. In response to prolonged stress, UPR loses the capacity to assist in protein folding and its dysregulation culminates with neuronal death as a protective measure to prevent further damage [40]. In this condition, the activation of C/EBP Homologous Protein by Protein Kinase R-like ER Kinase, Activating Transcription Factor 4 (ATF4) or ATF6 or X-box Binding Protein 1 appears to be central for the induction of ER stress-driven apoptotic signal, ensuring that cells with irreparable damage are eliminated to maintain tissue homeostasis. ER-phagy, a selective form of autophagy targeting the ER for degradation, plays a crucial role in the clearance of misfolded aSyn. The interaction with ER-resident autophagy receptor FAM134B and the involvement of calnexin are key components for the recruitment of unfolded aSyn, encapsulation of ER fragments into autophagosomes, transport to- and fusion with lysosomes, and degradation and clearance of misfolded synuclein [89].

2.4. Lipids

There is increasing evidence that the oligomeric high levels of polyunsaturated fatty acids (PUFA's) play an important role in neuronal toxicity. Notably, lipid peroxidation of PUFAs represents a feature of PD [90]. Specifically, there is a substantial increase in reactive aldehyde species such as malondialdehyde, 4-hydroxy-2-nonenal, cholesterol lipid hydroperoxide, and F2-isoprostanes in the SNpc of PD brain as well as in the anterior cingulate cortex of PD subjects [90,91].

Many studies also showed physical interaction between α Syn and PUFAs which results in a higher propensity to pathological aggregation [92–95]. The mutual electrostatic interaction between α Syn and membrane containing negatively charged lipids is found to affect the α Syn characteristics and membrane composition. In particular, changes in the levels of fatty acids, sphingolipids, and cholesterol have been reported [96].

2.5. Autophagic/Lysosomal Disruption

Autophagic/lysosomal disruption is closely linked to α Syn toxicity, particularly in the context of PD. Autophagy-lysosome pathway is a crucial mechanism deputy to degradation and recycling of damaged misfolded proteins, which include autophagosome formation, fusion with lysosomes and degradation by lysosomal hydrolases. Overexpression or aggregation of α Syn can disrupt the autophagy-lysosome pathway leading to the accumulation of misfolded α Syn in the brain, while, inefficient clearance of α Syn aggregates facilitates their spread to neighboring cells, propagating the proteotoxicity. The translocation of cytosolic α Syn to the lysosome lumen is mediated by binding of heat shock cognate 70 chaperone to the KFERQ sequence which, with other co-chaperones, directs the α Syn to the chaperone-mediated autophagy (CMA) adaptor Lysosomal-Associated Membrane Protein 2 (LAMP2A) located on the lysosomal membrane. Under stress conditions, exposure of the KFERQ motif can trigger CMA to remove harmful α Syn. Dysregulation of CMA is related to impaired degradation of α Syn and may contribute to the pathogenesis of PD [97].

Autophagy of mitochondria, or mitophagy, is intricately regulated by specific posttranslational modifications that “tag” the cargo for degradation, and by the Tank-binding kinase 1-mediated phosphorylation of *optineurin* that enhances its binding to ubiquitin and light chain 3 (LC3). Once bound to the ubiquitinated mitochondria, adaptors recruit LC3 so that the mitochondria are encapsulated by a double membrane structure called the autophagosome. Then, the autophagosome fuses with a lysosome forming an autolysosome, where the mitochondria are degraded and recycled [98]. Elevated α Syn levels inhibit macrophagic flux. Moreover, mutant forms of α Syn, such as A53T and A30P, exhibit a stronger binding affinity for LAMP2A which impairs the efficiency of α Syn clearance [99]. A53T and E46K α Syn variants also engage functional LC3B monomers into insoluble microaggregates on the surface of late endosomes favoring α Syn exosome excretion and seeding [79].

2.6. Metals

Although the precise role of metals in the pathogenesis of PD is still debated, multiple evidence suggest their involvement in conformational effects related to the binding of metal ions to α Syn and subsequent aggregation and accumulation. Elevated levels of metals such as iron, zinc, aluminum, lead, and copper have been found in the brain and in the cerebrospinal fluid (CSF) of PD patients [100]. Albeit with different affinities and stoichiometries, metals, especially copper, can establish electrostatic interactions with C-terminus of α Syn, more strongly with Tyr-125 and Ser-129 phosphorylate α Syn (p- α Syn), increasing their propensity to fibrillation. The aggregation speed of the acetylated A53T variant is higher with respect to wild type protein, suggesting an intrinsic self-assembly of the α Syn mutants into aggregates [101]. The toxicity of iron has also been investigated. Abeyawardhane et al. [102] suggest that the impact of Fe(II) on α Syn structure is higher than Fe(III) because its more elevated reactivity with O_2 which resulting in the production of H_2O_2 and triggering β -sheet generation; it act either as initiator and as a potential allosteric cofactor of protein misfolding [103]. α Syn interact with both oxidation states of copper ions (Cu(I) and (Cu(II)) generating ROS, and contributing to OS and potentially leading to aggregation into pathological fibrils [104]. Aluminum is a metal that can cross the blood-brain barrier (BBB) and accumulate in the brain [105]. It has been found to co-localize with Biondi ring tangles in PD brains [106]. There is evidence suggesting that aluminum can induce OS, or directly interact with α Syn, or disrupt the balance of essential ions in the brain, thus accelerating the fibrillation process of α Syn aggregation and contributing to the development and progression of PD.

3. Distribution of α Syn in Tissues and Fluids in Parkinson's Disease

The presence of different proteoforms of α Syn has been observed not only in the central nervous system (CNS) but also in peripheral tissues and biofluids such as cerebrospinal fluid, plasma, saliva, olfactory mucosa, skin, salivary glands, retina, adrenal medulla, heart, and gastrointestinal tract in PD cases, even if conflicting reports exist and regard the consistency and significance of this occurrence [107–109]. α Syn aggregates have been detected in various peripheral biopsies such as the gastrointestinal tract, skin, and salivary glands, even in the early stages of PD [110] supporting the hypothesis that PD might start in the peripheral nervous system before affecting the brain. For instance, α Syn pathology has been found in the enteric nervous system (ENS), leading to the theory that the disease may originate in the gut and then spread to the brain via the vagus nerve [111]. Similarly, skin biopsies have shown the presence of α Syn deposits, suggesting that peripheral tissues could serve as accessible sites for early diagnosis [110]. Peng et al. [112] showed that the presence of dermal phosphorylated α -syn serve the identification of the lesions in early stage of disease and predict clinical phenotypes. Figure 2 describes the different organs and tissues in which α Syn can be detected and used as biomarker for the development of diagnostic assays.-

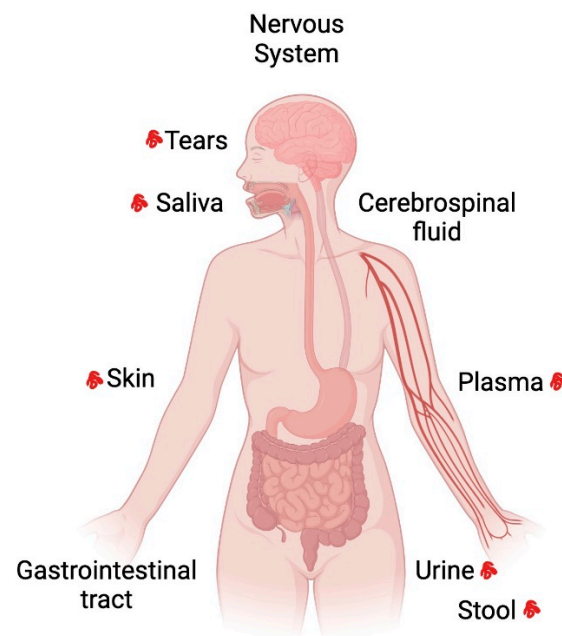


Figure 2. α Syn is distributed in different organs and tissues. Besides the central nervous system, α Syn aggregates can be observed in peripheral organs, tissues and biofluids. The detection in peripheral tissues (skin), biofluids (plasma, tears, saliva urine, stool) has made α Syn aggregates a biomarker for the development of non-invasive diagnostic assays. Created with Biorender.com.

However, studies have failed to consistently detect pathological α Syn in peripheral tissues of PD patients, raising questions about the reliability and specificity of these findings. For example, CSF α -synuclein inversely correlates with non-motor symptoms in a cohort of PD patients [41,113,114]. Differences in detection methods, sample handling, and the stage of the disease at which samples are collected could account for these discrepancies. Therefore, the presence of opposing data requires the development of standardized methodologies and more comprehensive studies for allowing peripheral α Syn become a robust biomarker for early diagnosis of PD and monitoring of disease progression [113].

4. Non-Motor Symptoms Associated with α Syn Pathology

Non-motor symptoms in PD include both sympathetic and parasympathetic dysfunctions and may concern, among others, neurobehavioral changes, pain, olfaction impairment, sleep and

circadian dysfunctions, gastrointestinal symptoms, uro-genital disturbances and cardiovascular problems.

Figure 3 describes the cardinal non-motor symptoms in the prodromal stage of PD.

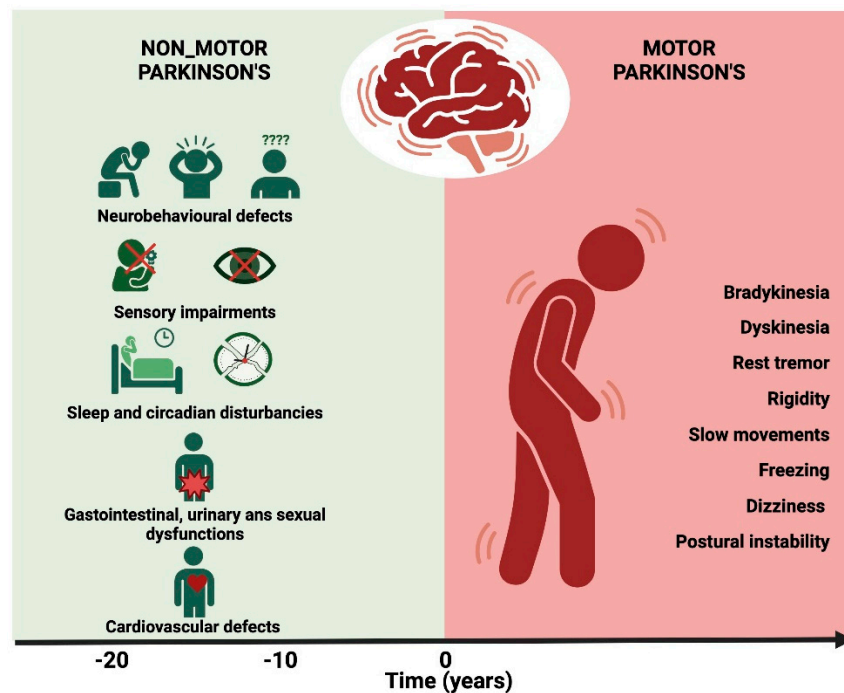


Figure 3. Prodromal non-motor symptoms in synucleopathies. In the prodromal stage of synucleinopathies, several non-motor symptoms, can appear up to 20 years before cardinal motor symptoms manifest. Created with Biorender.com.

4.1. Depression

The wide spectrum of NMS implicates the molecular interaction between the dopaminergic, glutamatergic, noradrenergic, and serotonergic systems in which a significant number of neurons are lost [115]. Depression is a psychiatric condition estimated to affect approximately half of all PD patients [116]. Around 17% recapitulate symptoms consistent with major depression [117,118]. Research indicates that α Syn pathology begins its early accumulation in the olfactory system, particularly in the anterior olfactory nucleus and then spreads to the limbic system. Moreover, neuroimaging studies revealed alterations in limbic system including cingulate gyrus, hippocampus, amygdala, hypothalamus, nucleus accumbens, ventral striatum, orbitofrontal cortex [119]. Unfortunately, L-DOPA, the gold standard for the motor symptoms treatment do not alleviate depressive symptoms, indicating that depression is associated with deficits in serotonergic neurotransmission in brainstem, raphe nuclei, and limbic system circuitry [120,121]. Serotonin and its metabolite, 5-HIAA, were decreased in the plasma of PD patients with depression [122]. Although the precise mechanisms for depression in PD are not fully elucidated, growing data reported the presence of aggregates of α Syn in monoaminergic brainstem, specifically in dendritic and axonal processes that, associated with loss of neurons in the above-mentioned brain areas, give rise to disturbances of neuroplasticity and depressive signs occurring in PD [123–125]. A recent study conducted in a mouse model of synucleinopathy showed that the overexpression of human α Syn in the raphe nuclei triggers progressive accumulation, phosphorylation, and aggregation of α Syn altering the 5-HT neurotransmission which results in a depressive-like phenotype [126].

4.2. Anxiety

Anxiety has a relative high prevalence (22.2%-66.7%) in PD patients with female being at higher risk than male patients [127–129]. Several kinds of anxiety are described in PD, including generalized anxiety, panic attacks, social phobia, agoraphobia, and obsessive-compulsive disorder. Stoyka et al. [130] showed that intrastriatal injections of fibrils of α Syn causes abnormal accumulation of α Syn inclusion in the cortex and amygdala. Likewise, injection of α Syn preformed fibrils into the bilateral olfactory bulb of A53T transgenic mice spreads into connected regions provoking severe pathology in the hippocampus, bed nucleus of the stria terminalis and central nucleus of the amygdala. Animals exhibited hyposmia, anxiety-like behavior, and memory impairment, consequence of atrophy, neuronal loss and gliosis [131]. Increase in hippocampal α Syn expression has been detected in rats with high levels of innate anxiety, suggesting that anxiety can cause α Syn accumulation, besides being a contributor of synuclein progression [129].

4.3. Psychosis

Psychosis is a premotor neuropsychiatric condition affecting PD patients, characterized by a spectrum of mental symptoms including illusions, delusions, visual hallucinations, schizophrenia (SCZ), and rapid eye movement sleep behavior disorder that are the result of dopamine hyperactivity in the mesolimbic pathway [132,133] and dysfunction of neurotransmitter systems [134]. In the past years, psychotic individuals such as schizophrenic treated with antidopaminergic and neuroleptic drugs manifested parkinsonism but not was actual PD patients. The use of atypical newer antipsychotic drugs has significantly reduced the incidence of the psychiatric symptoms [135]. On the other hand, PD psychosis (PDP) is a common side effect derived from dopamine use to treat motor symptoms. However, several data indicate that psychosis may predate motor signs even in absence of therapy and in PD patients and when manifested is associated with high mortality and morbidity and heavily impacts on the quality of life of many patients. There is controversial evidence about the role of α Syn in the pathophysiology of PDP. For example, studies reported downregulation of the α Syn expression [136] and lower levels of serum of α Syn in SCZ patients than healthy controls [137] while another study did not reveal significant differences between SCZ patients and healthy controls [138]. In one case study was found that duplication of the *SNCA* gene was associated with progression of PD [139]. Also, α Syn aggregates could contribute to neuroinflammation, OS, synaptic dysfunction and downstream neurotransmitter imbalance, the main feature of schizophrenia [140]. Furthermore, a pilot study revealed the association between rs356219 polymorphism in *SNCA* gene and psychiatric disorders [141] compared to healthy controls. Data from a human study described α Syn deposition in specific regions involved in directing attention toward visual target eliciting hallucination in dementia with Lewy bodies [142]. Furthermore, transgenic rats overexpressing human wild-type α Syn \downarrow (α Syn-BAC, harboring the entire human full-length *SNCA* locus) showed elevated levels of dopamine as a compensatory response, also accompanied by aberrant α Syn formation such as hyperphosphorylation, monomeric C-terminal truncation followed by aggregation pathology. These alterations produced a psychosis-like phenotype [133].

4.4. Cognitive Impairment

Cognitive decline is a prominent feature of PD and dementia with Lewy bodies (DLB), which comprises deficits that ranging from mild cognitive impairment to severe PD dementia (PDD).

It is noteworthy that α Syn directly impacts cognition and cognitive progression in PD. Many microRNA including miR-7, miR-129, miR-135a, miR-153 have been recognized to post-transcriptionally regulate α Syn levels involved in cognitive decline [143]. High CSF and plasma α Syn levels have recently been associated with higher prevalence of cognitive decline and faster progression of clinical dementia. Likewise, LB pathology evaluated by seed amplification assay [144–147] is associated with increased progression of DLB and rapid early alterations in cognitive performance [148]. These findings suggest a transport of CNS α Syn to the periphery which could help clinicians to detect by non-invasive practices α Syn levels as early as possible serving as a

potential surrogate biomarker of risk of cognitive impairment. A recent transcriptomic study in an α Syn-based brain model of PD shows region-specific gene expression changes associated with cognitive deficit [149].

4.5. Pain

Pain is a common uncomfortable NMS in PD which can develop many years before the onset of classic motor signs and significantly impacts on depression and patient's quality of life. It has been described in about 60-70% of patients and can be of different nature and prevalence. According to Ford's classification, five types of pain are proposed: musculoskeletal pain, radicular-neuropathic pain, dystonic pain, central neuropathic pain, and akathisia [150]. Central pathways involved in PD pain comprise the lateral pain pathways with projections to thalamus and primary sensory cortex, and the medial spinoreticulothalamic pathways intimately associated with autonomic nervous system, containing fibers that project to the medullary core and mesencephalon. Neuronal loss and Lewy body formation occur in medial pain pathway, specifically in parabrachial nucleus coeruleus and periaqueductal grey [151]. α Syn misfolding and aggregation may start in peripheral nerves fibers and spread alongside neuroanatomical sensory connections causing a multitude of painful perceptions [152].

In a spared nerve injury model of neuropathic pain, the expression of α Syn has been detected in peptidergic and non-peptidergic nociceptive neurons in the dorsal horn of the spinal cord, signifying an involvement in pain transmission in the CNS. In the same model, the inhibition of α Syn was associated with suppression of pronociceptive MAP kinase signalling [153]. In addition, Chen et al. [154] showed that δ -Opioid receptor activation attenuated the MPP(+) and hypoxia induced α Syn overexpression/aggregation by enhancing CREB phosphorylation and TORC1/SIK1/CREB pathways.

4.6. Olfaction Dysfunction

Olfactory dysfunction (OD) is an early NMS symptom of PD affecting more than 90% of patients whose underlying mechanisms is partly defined. Post-mortem studies of PD indicate that α Syn pathology starts in the OB and lower brainstem and developments in limbic system and connected brain regions leading to hyposmia [155].

Animal models created by injecting recombinant α Syn preformed fibrils in the bilateral OB exhibit Lewy Body-like pathology and OD [156,157]. Additionally, human A30P mutant α Syn-expressing mouse model causes OD along with reduction in OB neurogenesis and alterations in synaptic vesicular transport [158]. The induction of α Syn aggregates via overexpression of double mutant human α Syn (A53T and A30P) in OB, negatively impacts on neural activity and odor-evoked response in the OB [112]. A recent study using A53T mutant mice, revealed hyperactivity of mitral/tufted cells and disruption in excitation/inhibition balance in OB by impairing GABAergic transmission and abnormal expression of GABA transporters [159].

4.7. Visual Impairment

A variety of visual alterations, including ocular, visuoperceptive, and visuospatial impairments have been associated with PD. Therefore, eye movement, visual acuity, tritan axis of color perception, recognition of visual stimuli and spatial relationships between objects result strongly compromised [160]. α Syn aggregates and p-Syn positive Lewy body-like and neurites have been described in the retina of PD patients and correlates with motor scores at the stage of the disease [161]. Phosphorylated form of α Syn has also been detected in wholemount human retinal nerve fiber layer and ganglion cell layer from PD and PDD subjects. Importantly, α Syn accumulation in these structures leads to detrimental consequences on dopaminergic neuron functions [162]. Overall, these findings suggest that detecting α Syn in the retina could represent a promising approach for searching early marker of PD.

4.8. Sleep and Circadian Dysfunctions

Sleep and circadian dysfunctions are recurrent non-motor symptoms of synucleinopathies, and significantly correlate with poorer quality of life [163].

Among the most common sleep-wake disturbances there is rapid eye movement (REM) behavior disorder (RBD), a non-familial sleep disorder characterized by the loss of muscle atonia during REM sleep (REM sleep without atonia or RSWA) and dream-enactment behaviors [164]. RBD is strictly associated to synucleinopathies [165] to the point that idiopathic/isolated RBD (iRBD), that may precede the onset of motor features by decades, is considered a prodromal form of synucleinopathy and therefore a highly specific marker for future development of a synucleinopathy. Furthermore, α Syn aggregates are considered as a biomarker for the development of diagnostic assays. As example, α Syn aggregates in stool samples of iRBD patients can be detected and measured, supporting the diagnosis of prodromal synucleinopathies [166].

Transgenic mice overexpressing human A53T α -syn (SNCA^{A53T/-}) in its natively expressed regions exhibited REM sleep without atonia, similar to RBD patients, already at 5 months of age [167]. Compared to wild-type mice, in which REM sleep is characterized by sinusoidal theta-frequency electroencephalogram activity and absent or minimal electromyogram activity, SNCA^{A53T/-} mice displayed excessive muscle twitches in body and limb during REM sleep and transient increases in muscle activity [165,168,169].

Restless legs syndrome (RLS), a very common movement disorder manifested by disturbing symptoms in lower limbs, more severe in the evening or night, has a high prevalence in PD patients [170] and some studies report the onset of PD at younger age in subjects with RLS [171].

Insomnia and excessive daytime sleepiness (EDS) are also common in PD patients. Insomnia has been associated with depressed mood, autonomic symptoms fatigue and age [172]. Subjective EDS has been reported in up to 50% of patients with PD [169]; it has been associated to the neurodegenerative process itself, that is extended to the dopaminergic and non-dopaminergic neurons in the lower brainstem and midbrain [173] involved in sleep-wake regulation [174]. These observations of poorly consolidated rest/activity patterns in humans are paralleled by animal models. Rodent models for PD display impairment in the sleep-wake parameters, such as deficit in REM sleep, overwhelming episodes of sleep, similar to “sleep attacks”, increased sleepiness [175–177]. In *Drosophila*, the pan-neuronal overexpression of pre-fibrillar human α Syn oligomers impacts on the sleep-like rest behavior (defined as absence of movement for 5 consecutive minutes), in terms of number and length of sleep episodes and total sleep [178–181]. Flies exhibit decreased sleep (especially in the night), increased number of sleep bouts (indicating sleep fragmentation) and decreased wake activity [178,180,181]. These alterations precede the onset of motor symptoms and can be related to the presence of pre-fibrillar α Syn oligomers that prevent protein aggregation [178,179,181].

Sleep is coordinated by the interaction of homeostatic and circadian mechanisms, regulating the sleep debt and the periodicity of sleep/wake propensity, respectively [182]. Circadian rhythms are controlled by an endogenous mechanism that comprises: a pacemaker, orchestrated by interconnected transcriptional/translational feedback loops, input pathways for light and other stimuli that synchronize the pacemaker to the environment and output pathways that convert the molecular oscillation of clock components in overt rhythms [183]. In the primary loop, the molecular oscillation involves the transcription factors CLOCK and BMAL1, which, as heterodimer, regulate the rhythmic expression of output genes. The CLOCK/BMAL1 complex also activates the expression of the negative elements of the loop, Period and Cryptochrome genes, whose products inhibit their own expression by inactivating the activity of CLOCK/BMAL1 [183]. The circadian physiology is based on a hierarchical network of central and peripheral oscillators; the central pacemaker (master clock) is located in the suprachiasmatic nuclei (SCN) of the hypothalamus: it receives signals from the environment and transmits temporal information to downstream peripheral clocks, located in organs such as heart, lungs, liver and adrenal glands, through neurotransmitters and neuromodulators [183]. Melatonin secretion is a rhythmic output generated by the SCN: melatonin

and circadian clock gene expression can be easily measured in serum and peripheral blood mononuclear cells, respectively, serving as reliable markers of circadian rhythmicity [183].

Several studies have reported lower levels and dampened melatonin oscillation and a lack of time-dependent variation in Bmal1 expression in PD patients, compared to healthy controls, indicating that the peripheral molecular clock is affected in PD [94,169,184].

Also, in *Drosophila*, the sleep defects reported in flies overexpressing pre-fibrillar human α Syn oligomers are associated with a severe impairment of two key circadian features, the anticipation of the dark/light transition and the circadian periodicity [178].

4.9. Gastrointestinal Symptoms

For a long time α Syn has been identified as an important player in the complex process leading to GI symptoms in PD. Several large cohort and case-control studies show correlations between gastrointestinal (GI) dysfunctions and PD, DLB, and PDD during the disease course and overlap with autonomic symptoms [185,186].

GI disorders can cause PD on one hand and increase the risk of developing PD on the other two distinct subtypes of PD have been initially proposed based on the origin and progression of α Syn pathology: a “brain-first” subtype, in which α Syn pathology originates in the OB or other brainstem regions and then spreads to the peripheral autonomic nervous system, and a “body-first” subtype in which the pathological process starts in the ESN and then ascends via the vagus nerve or other autonomic pathways to reach the brain [187]. However, recent post-mortem studies showed that Lewy pathology is triggered in the GI tract or autonomic nervous system without concomitant involvement of the OB, therefore supporting a single-hit brain-first hypothesis [188,189].

Loss of enteric dopamine cells and degeneration of vagus nuclei represent the main cause of GI symptoms such as dysphagia, sialorrhea, bloating, nausea, vomiting, gastroparesis, and constipation.

p- α Syn deposited in vagus nerve Schwann cells resulting in inflammatory response induced by interaction and activation with a family of pattern recognition receptor, Toll-like receptor 2 (TLR2), implicated in regulation of α Syn release [190]. On the other hand, the interaction between p- α Syn and TLR2/4 has been previously described in murine models of PD as well as in post-mortem human PD brain and associated with pro-inflammatory response and PD pathology [191,192].

GI symptoms affect nearly 80% of subjects before or after onset of motor manifestations and some of them are life-threatening symptoms, as an example dysphagia, due to the risk of pneumonia. Furthermore, PD patients experience a more widespread onset of lifelong GI symptoms and constipation is widely recognized as one of the most prevalent NMS of PD. Intestinal microbiome also plays a role in the bidirectional communication between the brain and the gut that has emerged as a significant aspect of PD pathology [193–195].

Aberrant aggregation of α Syn is responsible for vagus nerve and ENS degeneration, slow down intestinal peristalsis, and constipation [196,197]. A study revealed that human A53T α Syn transgenic mice exhibit severe signs of GI dysfunction together with α Syn aggregation in the ESN [198]. Interestingly, it has also been shown that pathological species of α Syn can be carried through red blood cells extravesicles to the GI tract, contributing to the onset and/or progression of the PD pathology.

In recent years, some authors speculate about the role of short-chain fatty acids (SCFAs) produced by the gut microbiome, especially butyrate and propionate, on development of synucleinopathies. Paradoxical and contracting effects of SCFAs were obtained, probably depending on the injection route ways, the mixture composition and concentration [199–202]. For example, lower SCFA levels and higher calprotectin quantity detected in stool of PD patients correlate with GI symptoms [203]. An interesting preclinical study conducted in α Syn pre-formed fibrils (α Syn PFFs)-induced rat model of PD, documented the protective effects of sodium butyrate by reducing inflammatory markers such as TNF α , IL-1, IL-6, and increasing DA content [204]. Moreover, fecal transplant of gut microbiota from PD patients to α Syn overexpressing mice seems to promote α Syn-dependent activation of microglia and motor deficit worsening [205].

4.10. Sexual Dysfunction and Urinary Dysfunction

Sexual and urinary dysfunctions are common NMS in PD patients that involve neuronal cytoplasmic α Syn inclusions in the peripheral autonomic small nerve fibers. In about 70% of subjects, nocturia accompanied by urge urinary incontinence and detrusor hyperactivity often followed by the appearance of motor symptoms [206,207]. Sexual performance and relationship dissatisfaction have evaluated by employing multidimensional self-administered questionnaires. Data analysis suggest that there is a high prevalence of sexual dysfunction among young-onset male PD and female compared to healthy subjects [208], which is related to severity of depressive symptoms especially in female [209]. A number of studies have shown a range of symptoms ranging from hyposexuality to hypersexuality behaviors. For example, erectile dysfunction has been reported in diagnosed male PD and DLB cases, and loss of libido and orgasmic dysfunction were found in both women and men [210] while hypersexuality behaviors are often associated with PD treatment [201]. Impairment in courtship rituals and in copulation were observed also in a *Drosophila* A30P-mediated PD model [211].

4.11. Cardiovascular Symptoms

Epidemiological studies have suggested a possible relationship between the incidence of cardio-cerebrovascular disease and PD, either as risk factors or as manifestations of PD itself [212,213]. Studies using Mendelian randomization method reveal that PD is correlated to high risk of coronary artery disease, stroke, ischemic stroke, and cardioembolic stroke compared with age- and gender-matched general population [214,215]. On the other hand, the deposition of α Syn in the brain of PD may be a potential pathogenic factor for cardiovascular disease and stroke [216]. The involvement of the cardiovascular system in PD reflects α Syn deposition in sympathetic noradrenergic nerves, defects of the autonomous cardiac innervation and abnormal function of residual noradrenergic endings [217,218].

The loss of myocardial noradrenergic innervation together with the loss of myocardial norepinephrine caused by Lewy bodies deposition, are responsible for orthostatic hypotension with substantial fall in systolic and diastolic blood pressures of at least 20 mmHg and 10 mmHg, respectively, during the change from supine to standing position [219]. In PD patients a significant alteration in the electrophysiological activity and remodeling of the myocardium has also been described [220]. PD entails α Syn multi-organ deposition including myocardial tissue signifying that α Syn fibrils dispersed in the myocardium may be pathogenic. Myocardial tissues from PD autopsies display p- α Syn deposits and Lewy body pathology which correlate with cardiac sympathetic denervation [221]. Accumulation of α Syn aggregate in the paravertebral sympathetic ganglia seems to be chronologically preceded by those in the distal axons of the cardiac sympathetic nervous system, suggesting centripetal degeneration [222]. To note, cardiac dysfunction can be present even when the CNS α Syn deposition is limited to the brainstem only, with doubtless no clinical symptoms [223,224].

5. Conclusions

Given the growing incidence and the long list of NMS in the prodromic stage of PD, that negatively impact on health-related quality of life, it is imperative for clinicians to achieve an early diagnosis aimed at prompt intervention to alleviate the symptoms and hopefully to slow the progression of the disease. The correlation between α Syn deposit and the appearance of NMS in the 2- to 20-year pre-motor period is well-documented, although the exact mechanisms have to be fully elucidated. Interestingly, the possibility to detect and quantify α Syn conformers in biofluids and in tissue biopsies reflects the multisystem nature of the disorder and represents a promising diagnostic approach at preclinical PD stage, when neurodegeneration starts. Randomized controlled trials, cohort studies/cross-sectional studies and the validation of PD-specific screening questionnaire together with non-invasive and painless withdrawal procures and sophisticated technology for α Syn measurement could contribute to achievement of timely diagnosis, monitoring and management of PD.

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