Identification of Dysautonomia in Parkinson's Disease Based on Braak Neuropathological Stages

Identificação de disautonomias na doença de Parkinson com base nos estágios neuropatológicos de Braak

Leonnardo Altoé Miranda Lemos[1], Ana Julia Lustosa[1], Bruno Almeida Lara Miranda[2], Elize Cândido de Farias[1], Gabriel Silvério[3], Gustavo Lucas Mernick[1], Izabelly Constantinov Lemos[1], Rafael Alexandre dos Santos[1]

[1]Medical Student, Centro Universitário Campo Real, Guarapuava, Paraná, Brazil;
[2]Department of Medicine, Centro Universitário Campo Real, Guarapuava, Paraná, Brazil;
[3]Hospital São Vicente de Paulo, Neurology Department, Neurologist, Guarapuava, Paraná, Brazil.

ABSTRACT

Introduction: The Autonomic Nervous System regulates important functions in the body's organic systems, such as the cardiovascular, gastrointestinal, urogenital and thermoregulatory components. Failures in this fundamental homeostatic component result in dysfunctions, known as dysautonomias, which lead to the manifestation of various clinical signs and symptoms. In patients with Parkinson's disease, it is possible to determine the progression of dysautonomia by identifying the structures affected by α-synuclein accumulation by means of Braak neuropathological stages.
Objective: The aim of this article is to identify, through Braak stages, the possible involvement of central and autonomic structures that lead to the initial recognition of dysautonomias, which enables a more accurate diagnosis of the pathological progression of Parkinson's disease.
Methods: This article is a Narrative Review approach whose methodology was based on the PRISMA research method. The article presents the identification of central and autonomic areas that lead to dysautonomia in Parkinson's disease based on Braak neuropathological stages.
Results: Based on Braak neuropathological stages, it was possible to identify that the involvement of central and autonomic structures by Lewy bodies can lead to dysautonomia in Parkinson's disease. This condition appears to follow a pattern of manifestation in the early stages of the disease and, in most cases, may precede classic motor symptoms.
Conclusion: Based on the theoretical foundation of the research, it can be concluded that the application of Braak neuropathological stages for the recognition of central and peripheral structures affected by Lewy bodies is useful for confirming disease progression, contributing both to a more accurate diagnosis and to more appropriate clinical management.

Keywords: Dysautonomia; Parkinson Disease; Autonomic Nervous System; Lewy Bodies; alpha-Synuclein.

RESUMO

Introdução: O Sistema Nervoso Autônomo regula importantes funções no sistema orgânico do corpo, como os componentes cardiovascular, gastrointestinal, urogenital e termorregulatório. Falhas nesse fundamental componente homeostático resultam em disfunções conhecidas como disautonomias, as quais levam à manifestação de diversos sinais e sintomas clínicos. Em pacientes com a doença de Parkinson, há a possibilidade de determinar a progressão das disautonomias pela identificação de estruturas acometidas pelo acúmulo de α-sinucleína por meio dos estágios neuropatológicos de Braak.
Objetivo: O objetivo deste artigo é identificar, mediante os estágios de Braak, o possível envolvimento das estruturas centrais e autonômicas que levam ao reconhecimento inicial das disautonomias, o que permite um diagnóstico mais preciso da progressão patológica da doença de Parkinson.
Métodos: Este artigo é uma abordagem de Revisão Narrativa cuja metodologia foi fundamentada no método PRISMA de pesquisa. O artigo apresenta a identificação de áreas centrais e autonômicas que levam à disautonomia na doença de Parkinson com base nos estágios neuropatológicos de Braak.
Resultados: Com base nos estágios neuropatológicos de Braak, foi possível identificar que o acometimento de estruturas centrais e autonômicas podem levar às disautonomias na doença de Parkinson. Tal condição aparenta seguir um padrão de manifestação nos estágios iniciais da doença, podendo, na maioria dos casos, anteceder os sintomas motores clássicos.
Conclusão: A partir do embasamento teórico da pesquisa, pode-se concluir que a aplicação dos estágios neuropatológicos de Braak para o reconhecimento de estruturas centrais e periféricas acometidas pelos corpos de Lewy é útil para confirmar a progressão da doença, contribuindo, tanto para um diagnóstico mais preciso, quanto para um manejo clínico mais adequado.

Palavras-chave: Disautonomia; Doença de Parkinson; Sistema Nervoso Autônomo; Corpos de Lewy; alfa-Sinucleína.

ARTICLE INFO

DOI: https://doi.org/10.46979/rbn.v62i2.73036

Corresponding author:
Leonnardo Altoé Miranda Lemos; Rua Comendador Norberto, 1299.
Email: med-leonnardolemos@camporeal.edu.br.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Support: This work has not received any contribution grant or scholarship.

Authors' contributions:
LAML: conceptualization, data curation, project management, supervision, writing - original draft, writing - revision and editing. AJL: conceptualization, writing – original draft. BALM: conceptualization, writing – original draft. ECF: conceptualization, writing – original draft. GS: conceptualization, reviewer - original draft. GLM: conceptualization, writing – original draft. ICL: conceptualization, writing – original draft. RAS: conceptualization, writing – original draft.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease, defined by clinical and anatomopathological criteria. Described by James Parkinson in 1817, it was clinically characterized by the presence of two or more of the following symptoms: resting tremor, bradykinesia, muscle rigidity and postural instability.[1] However, currently, the new definition of the diagnostic criteria for PD is the presence of bradykinesia accompanied by rigidity and/or tremor.[2] The Autonomic Nervous System (ANS) consists of at least five components, such as: Enteric Nervous System, parasympathetic cholinergic, sympathetic cholinergic, sympathetic noradrenergic and adrenomedullary hormonal.[3] The involvement of any of the autonomic components mentioned above can cause the presence of characteristic clinical manifestations, known as dysautonomia.

The association between PD and dysautonomia/dysfunction of the ANS is a phenomenon reflected in the clinical manifestations of the disease, such as hyperhidrosis, dysphagia, gastroparesis, autonomic anorectal dysfunction, vasomotor disorders, bladder dysfunction, sexual impotence, orthostatic hypotension and thermoregulatory dysfunction.[4] Therefore, it is believed that the involvement of the ANS is related to the development of the disease, the medications used to treat it (dopaminergic agonists, levodopa) or the combination of these factors.[5] Furthermore, it is also known that the ANS is compromised with aging, which reinforces the loss of its ability to regulate physiological mechanisms in PD.[6]

The main neuropathological features of dysautonomia present in PD are autonomic neuronal destruction and α-synuclein accumulation. Autonomic neuronal destruction is defined by the loss of neurons, degeneration of nerve fibers and synaptic loss.[7] Excess of α-synuclein can probably be represented by the formation of Lewy bodies, which remains unclear due to the incomplete understanding of its pathophysiology.[8] Thus, parkinsonian patients present Lewy bodies, both in the neurons of the Central Nervous System (CNS) and in the pre and postganglionic neurons of the ANS.[9] It is believed that the impairment of these areas might be related to the excess of α-synuclein that occurs, firstly, in the ANS, reaching the brain bilaterally through vagus nerve and then spreading throughout the CNS.[10]

In this context, it can be inferred that the dysautonomias present in PD are associated with the presence of multiple functional alterations, notably cardiovascular, gastrointestinal, urogenital, cutaneous and thermoregulatory changes.[11] Such occurrences can be explained by the approach that PD is a multisystemic neurodegenerative process, affecting not only the dopaminergic pathways, but also the cholinergic, noradrenergic and serotonergic pathways.[12]

Therefore, to propose a possible evolution of the pathological progression of PD, Braak neuropathological stages were developed. According to these stages, the involvement of central structures affected by Lewy bodies demonstrates that the pathological progression of PD begins in the lower brain stem (bulb).[13] Thus, the duration of each stage of the disease is variable, as is the order of appearance of the non-motor symptoms.[14] As a result, it is assumed that the presence of Lewy bodies establishes the pathological evolution of PD due to the increase in the number of these bodies and, consequently, their appearance in new central and autonomic structures, leading to neuronal degeneration.

In this sense, the present article aims to identify, through Braak stages, the involvement of central and autonomic structures that lead to the initial recognition of dysautonomias, which may contribute towards a more accurate diagnosis of the pathological progression of Parkinson's disease.

METHODS

This article is a Narrative Review approach. The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) methodology was used to filter the articles to be used. The following keywords were applied in the Biblioteca Virtual em Saúde[15] (BVS) system to obtain articles related to the topic: (''Parkinson's Disease'' AND ''Braak stages'') and (''Autonomic Dysfunction in Parkinson's Disease''). The articles presented by the BVS system were then analyzed using the following inclusion criteria: articles published between 2022 and 2025, in English, articles related to the theme covered. The exclusion criteria were: articles from other periods, other languages, unrelated to the theme covered. Such filters were applied to the BVS system so that it was possible to obtain international and updated articles for the elaboration of the research. Priority was given to original scientific articles, reviews and some case reports. Thus, after this screening, 571 articles were analyzed, of which 82 were included for further analysis. At the end of the article analysis process, 6 were included and 489 were excluded. Figure 1 shows the main points of the methodology described.

The articles classified as ''Original Research'' in Figure 1 were added to the search because of the wide range of dysautonomias resulting from Parkinson's disease, making it impracticable to filter them by keywords, as in the BVS system. For these articles, a research was conducted using the following platforms: PubMed, SciELO and Google Scholar. The following inclusion criteria were applied: articles related to the theme "Dysautonomias in Parkinson's disease". The exclusion criteria were: nonconformity with the proposed theme. There were no restrictions on both date and language of publication of these articles. The included articles for this section are identified as numbers

due to their respective chronological order of citation used in the references of this work.

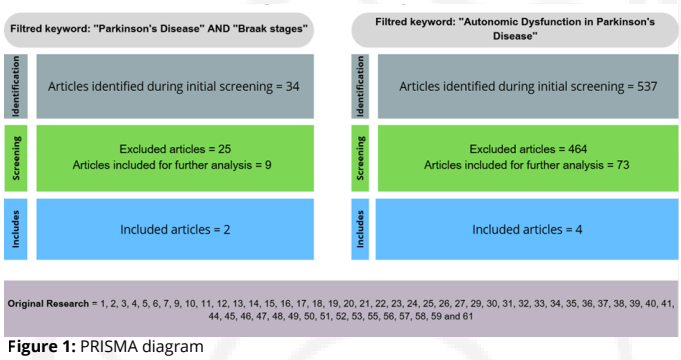

Figure 1: PRISMA diagram

RESULTS

The formation of Lewy bodies in PD may be one of the determining factors of neuronal degeneration and excess of α-synuclein in the Central and Autonomic Nervous Systems. Thus, in order to identify the central and autonomic structures affected by the pathological development of Lewy bodies, Figure 2 was proposed. This figure contemplates, through Braak stages, the possible progress of these bodies in the mentioned regions with their probable clinical developments.

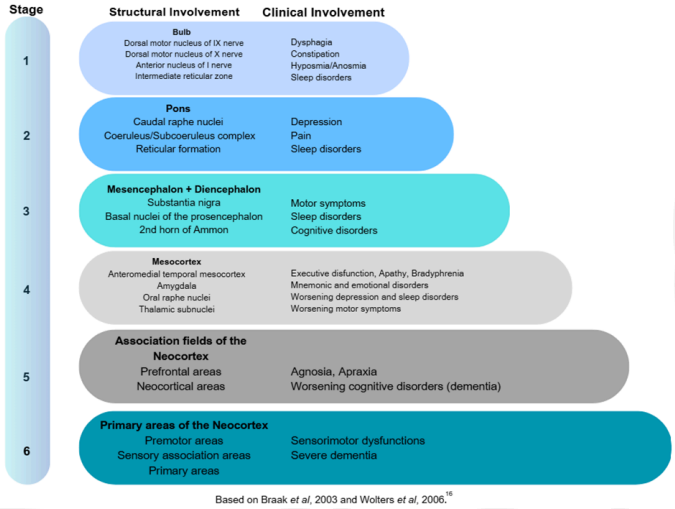

Figure 2 - Possible pathological progression of Parkinson's disease with its probable clinical and anatomic involvements

Stage 1

The structures that demarcate the beginning of PD progression (stage 1) are the structures related to the bulbar area (dorsal motor nucleus of the IX and X nerves, anterior nucleus of I nerve, intermediate reticular zone).[13] At this stage, Parkinson's patients tend to, initially, present some non-motor symptoms, notably the onset of dysautonomia, such as dysphagia and constipation.[7] These dysautonomias can be explained by the involvement of the glossopharyngeal and the vagus nerve nuclei due to the increasing progression of Lewy bodies.

The dorsal motor nucleus of the vagus has acetylcholine as a neurotransmitter. The presence of failures of these cholinergic neurons is expressed by the symptoms of constipation.[1] It is known that 20% of elderly people with PD present this symptom. In that regard, it is suggested that constipation may be one of the first symptoms preceding the classic motor symptoms of the disease by at least 10 years.[17] The same mechanism of the cholinergic neurons alteration can be applied to the glossopharyngeal nerve, in view of the fact that the central cholinergic dysfunction is related to the dysphagia in the initial phase of PD.[18]

The implication of failures in the intermediate reticular zone, whose neurotransmitters are noradrenaline and acetylcholine, contribute to sleep disorders.[1] This fact is due to the impairment of these neurotransmitters, causing: insomnia, sleep fragmentation, early awakening, vivid dreams, nightmares and rapid eye movement behavior disorder (RBD).[16]

Lesions in the anterior olfactory nucleus, which has norepinephrine as a neurotransmitter, result in symptoms of hyposmia/anosmia.[1] The prevalence of olfactory dysfunction in parkinsonians varies from 70% to 90% of cases; it may be, like constipation, a years-long antecedent to the classic parkinson symptoms.[19]

Stage 2

Stage 2 is demarcated by the involvement of structures in the pons region, such as the caudal raphe nuclei (magnus, obscurus and pallidus), reticular formation (gigantocellular nucleus) and locus coeruleus/subcoeruleus nuclei.[13]

The serotonergic cells of the raphe nuclei, through the limbic system, exert their functions in regulating mood.[1] Thus, possible damage to these structures may favor serotonin deficiency, comprising the symptoms of depression indicative of this stage.[16]

The reticular formation, when affected in stage 2, keeps causing sleep disorders. It is clear that sleep disorders are identified in 80% to 90% of parkinsonians.[20] In the case of RBD, it is reported that it causes motor manifestations in 52% of PD cases.[21]

Coeruleus/Subcoeruleus complex, noradrenergic, is involved in the pain inhibition process. In addition to this structure, anterior cingulate gyrus, insular cortex, median nucleus of the thalamus, amygdala and hypothalamus are also part of pain regulation, but the involvement of these other structures is only reported in more advanced stages of PD.[1] In parkinsonians, primary central pain constitutes one of the non-motor manifestations, occurring in 67% of these patients.[22]

Stage 3

As Lewy bodies rise through the lower ortion of

the brainstem, the limit of the pontine tegmentum is exceeded, now spreading to the basal parts of the mesencephalon and the prosencephalon.[16]

Thus, stage 3 is characterized by being the only one of the six stages in which there is recognition of the first Lewy bodies in the compact part of the substantia nigra, basal magnocellular nuclei of the prosencephalon (medial septal nucleus, interstitial nucleus of the diagonal band and basal nucleus of Meynert) and 2nd sector of Ammon's horn.[13]

In the substantia nigra, dopaminergic neurons synthesize dopamine, which, when transported through the nigrostriatal pathway, is stored in the striate nucleus, specifically in the putamen. The impairment of dopamine has repercussions on the motor symptoms of PD (tremor, rigidity and bradykinesia), which occur later, only after 60% of cell loss.[1]

The basal magnocellular nuclei of the prosencephalon, mediated by acetylcholine, are associated with cognition and the sleep-wake cycle.[1] Thus, sleep disorders and cognitive changes (inattention and drowsiness) can be accompanied by motor symptoms. As far as the 2nd sector of Ammon's horn is concerned, amnestic disturbances can be associated with the impairment caused by Lewy bodies.[16]

Stage 4

Stage 4 is related to the presence of Lewy bodies in the anteromedial temporal mesocortex, basolateral subnuclei of the amygdala, oral raphe nuclei (linearis, centralis and dorsalis), claustrum, interstitial nucleus of the stria ter minalis and many thalamic subnuclei; preserving the neocortex.[13]

The anteromedial temporal mesocortex mediates the transfer of connections between the sensory neocortex, through the amygdala, entorhinal cortex and hippocampus pathways; with the prefrontal neocortex. Thus, the impairment of this neocortico-limbic-neocortical system, which is essential for the selective processing of information, is a contributor to the occurrence of bradyphrenia, apathetic behavior, executive and mnemonic dysfunctions.[13] Cases of emotional and mnemonic dysfunction may be more closely related to the basolateral subnuclei of the amygdala.

In relation to raphe's oral nuclei, there is a worsening of the manifestations related to depression and sleep disorders.[16] In this case, the worsening of such symptoms may be related to the fact that there is a more pronounced depletion of serotonergic neurons because they have already been affected since stage 2.

Stage 5

From this stage onwards, there is a progression of neuropathological changes, going from the temporal mesocortex to the neocortex.[16] Lesions in subcortical and mesocortical structures continue to progress. The few remaining dopaminergic neurons of the substantia nigra are practically devoid of dopamine, a fact demonstrated by the pallor of these structures during macroscopic inspection. Furthermore, 1st order areas of sensory association, premotor areas, primary sensory area and primary motor area do not have, yet, the presence of Lewy bodies, a fact that only occurred with stage 6.[13]

The advent of Lewy body progression affects, at this stage, sensory association areas of the neocortex, prefrontal neocortex, granular and agranular insular cortex, 1st and 3rd sectors of Ammon's horn, and cortex of the anterior cingulate gyrus.[13]

In this context, due to the installation of Lewy bodies in the neocortical region, the beginning of the dementia process is evident, as there is worsening of cognitive conditions with added agnosia and apraxia now.[16] These symptoms could be related to the prefrontal region, which is responsible for interpreting decisions.

Stage 6

The main characteristic of this advanced stage of PD is, practically, the thorough involvement of the Neocortex. At this stage, there is diffuse involvement of the primary cortical areas, such as premotor, motor (primary motor area) and sensory areas (areas of sensory association and primary sensory area).[13]

In this sense, in addition to the worsening of manifestations related to previous stages, there is an intensification of motor symptoms, leading the patient to orthostatic incapacity. Furthermore, other symptoms that are also expressed in an aggravated form in stage 6 are hallucinations and delusions, both of which as consequences of behavioral and cognitive declines.[1] Such manifestations can contribute to the intensification of the dementia process; enabling this condition to reach an advanced stage.

However, it is important to emphasize that the temporal relationship between the onset of dementia and parkinsonism is crucial for differentiating dementia with Lewy bodies (DLB) from Parkinson's disease dementia (PDD). This chronological distinction is widely recognized as the "1-year rule". According to this rule, DLB occurs before or simultaneously with the onset of motor symptoms, whereas PDD develops at least one year after the onset of parkinsonism. In addition to this chronological criterion, DLB may present early typical clinical features, such as fluctuating cognition with pronounced variations in attention and alertness; recurrent visual hallucinations that are typically well-formed and detailed; RBD, which may precede cognitive decline; and one or more spontaneous cardinal features of parkinsonism (bradykinesia, resting tremor, or rigidity).[23] These signs and symptoms therefore contribute significantly to the clinical differentiation

between these conditions.

In this context, the progressive involvement of the above-mentioned structures contributes to the development of peripheral alterations resulting from ANS dysfunctions in various systems of the body. Autonomic alterations as well as their respective clinical and structural disorders will be hereinafter analyzed with a view to identifying, through this analysis, their possible relation with the Braak stages, whose aim is a more accurate PD diagnosis.

DISCUSSION

The pathological involvement of Lewy bodies in central areas may be reflected in a systemic and complex aggravating clinical manifestation of ANS, the dysautonomia. Dysautonomias are expressed through multiple dysfunctions in body systems, notably gastrointestinal, cardiovascular, urogenital and thermoregulatory. Such dysfunctions and their respective symptoms are displayed in Figure 3.

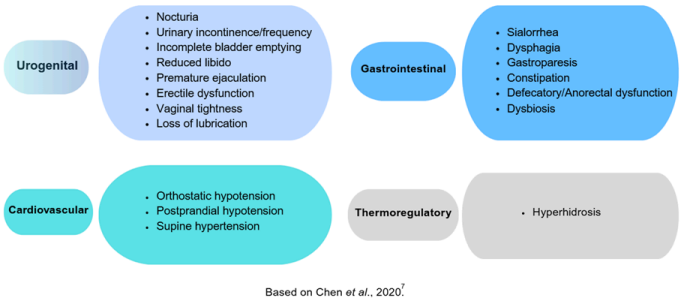

Figure 3 - Types of dysautonomic dysfunctions with their respective clinical manifestations affected by Parkinson's disease

Dysautonomic Clinical Manifestations

1. Gastrointestinal Dysfunctions

Gastrointestinal dysautonomias can be attributed to the degenerative process of various structures of the ANS, such as vagus nerve, enteric plexuses, peripheral sympathetic nerve and sacral parasympathetic nerve.[7] An example of this degenerative process is the reduction in size of vagus nerve axons in patients with PD.[24] Thus, the involvement of these structures results in loss/reduction of intestinal mobility, which contributes to the development of multiple gastrointestinal disorders.

In this sense, the dysautonomia manifestations related to the gastrointestinal dysfunction include: dysphagia, gastroparesis, constipation and autonomic anorectal dysfunction. In view of the fact that dysbiosis and sialorrhea are secondary impacts of such manifestations, they will not be addressed in detail for not representing direct dysautonomias. However, it is pivotal to highlight that they can occur at any stages of PD, mainly at more advanced stages.

1.1 Dysphagia

Dysphagia occurs in 11% to 81% of PD patients.[25] This adversity has been presented in both the pre-oral and oral phases (mandibular rigidity; motor alterations in the lingual, cervical and extremity portions), with a delay in the pharyngeal phase due to hypertonia of the upper esophageal sphincter.[26] These causes are due to muscle rigidity and bradykinesia, resulting in a delay in the swallowing reflex and reduced mobility of the oropharyngeal structures.[27] Thus, the first signs of dysphagia may occur in the early stages of PD, but it tends to be more noticeable only in more advanced stages.[28]

The axons of the ambiguus nucleus perform the motor innervation function of swallowing, involving muscles of the pharynx, upper esophagus and intrinsic muscles of the larynx. The nucleus of the solitary tract is also involved with swallowing and it integrates vagal sensory information to assist in the synchronization of peristaltic activity during swallowing.[28] According to Braak stages, these brainstem regions, which are responsible for swallowing, are connected to the caudal regions of the brainstem that are affected early in the progression of the disease.[13]

Thus, the onset of dysphagia may be related to Braak stage 1. This conclusion tends to be presumed given that the structures mentioned may be related to the depletion of cholinergic neurons present in this early stage of PD, as is the case with the glossopharyngeal and vagus nerve nuclei.

1.2 Gastroparesis

Currently, the most accepted definition for gastroparesis is the presence of appropriate symptoms (nausea, vomiting, early satiety and postprandial fullness) for ≥12 weeks, together with a delay in gastric emptying and the absence of gastric obstructive lesions.[29] Its exact prevalence in PD remains unknown.[7]

In this sense, the regulation of gastric control comes from the vagus nerve and the Enteric Nervous System (ENS). The ENS consists of 2 ganglionated nerve plexuses: the submucosal (Meissner's) plexus and the myenteric (Auerbach's) plexus. In the stomach, the myenteric plexus is directly connected to the afferent and efferent vagal pathways, which influence gastric control. Thus, during the premotor phase of PD, the dorsal motor nucleus of the vagus appears to be compromised by Lewy bodies, making it pertinent that gastroparesis may be present in the early stages of the disease.[30]

As shown in Braak stage 1, the dorsal motor nucleus of the vagus appears to be affected by the progression of Lewy bodies, causing cholinergic depletion. Such depletion may be responsible for the loss/failure of vagal control in the myenteric plexus, corroborating that the onset of gastroparesis is related to Braak stage 1.

1.3 Constipation

Intestinal constipation is defined, according to the ROME IV criteria, as the presence of at least two of the following criteria: straining to defecate, presence of hard or irregular stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage during defecation, use of digital maneuvers to facilitate defecation and decrease in stool frequency to less than three bowel movements per week.[31] Such constipation symptoms have been diagnosed in 20% to 70% of Parkinson's patients.[32] Several factors can contribute to the occurrence of constipation in PD, such as the progression of the disease itself, intestinal motility and reduced water intake.[33] Thus, due to the fact constipation regularly occurs in the premotor phase of PD, this symptom it was included as a prodromal marker in PD.[34]

In this context, it is suggested that constipation, as mentioned previously, may precede the classic motor symptoms of the disease by at least 10 years.[17] This fact was notably presented by Braak, who demonstrated new evidence regarding the accumulation of α-synuclein in the submucosal and myenteric nerve plexuses of the ENS.[35] From then on, investigation by intestinal biopsy was motivated by the observation that constipation was an early non-motor characteristic of PD.[36]

Currently, it is known that, in addition to the ENS, the dorsal motor nucleus of the vagus may also be affected by the accumulation of α-synuclein early in the disease.[37] This fact emphasizes the theory that peripheral vagal connections with the ENS plexuses are responsible for the progression of Lewy bodies to central level structures.[10] Thus, the pathological progression of PD by Braak can be applied in this case, since the involvement of the dorsal motor nucleus of the vagus can contribute to the expression of constipation in initial stages.[1] In this sense, analyzing this vagal involvement, constipation may initially be associated with Braak stage 1.

1.4 Defecatory/Anorectal dysfunction

Defecatory/anorectal dysfunction is characterized by increased straining during defecation, painful defecation and incomplete emptying. These symptoms of anorectal dysfunction may be present in 61% to 67% of individuals with PD. Furthermore, these symptoms may be evident in both the early and advanced stages of the disease.[3]

Physiologically, defecation occurs through the relaxation and contraction of structures. Relaxation of the puborectalis muscle, internal and external anal sphincters aligns the rectum and widens the anorectal angle, facilitating bowel movements. Thus, during the relaxation of these structures, the abdominal, diaphragmatic and gluteal muscles contract, increasing intra-abdominal pressure to facilitate bowel movement. In this sense, in PD, there is a failure in the coordination of these muscular and sphincter structures, resulting in inadequate relaxation of the internal and external anal sphincters, inability to open the anorectal angle and inadequate generation of abdominal pressure, promoting, as a consequence, difficulty in defecating.[38] This loss of coordination of anorectal structures may be related to the direct involvement of ENS neurons by the accumulation of α-synuclein.[39]

In this context, as well as the gastrointestinal dysfunctions mentioned, anorectal dysfunction may also be associated with Braak stage 1. Similar to what occurs in intestinal constipation, the early accumulation of α-synuclein in the submucosal and myenteric plexuses of the ENS can both compromise local autonomic regulation and contribute to the progression of the pathology to the vagus nerve. This progression of the pathology can facilitate advancement to the brainstem, affecting structures at central levels, such as the dorsal motor nucleus of the vagus. Thus, indirectly related to this process, there is a loss of vagal influence on the sympathetic and parasympathetic pathways of the ENS that modulate anorectal function, contributing to defecatory dysfunction.

2. Cardiovascular Dysfunctions

The reflex arc of the circulatory system's baroreceptors perceives, by means of mechanoreceptors, changes in blood flow, transmitting them to the brainstem via IX and X nerves (afferent responses). Through solitary tract, these pairs of nerves make connections with cortical centers that send efferent responses to the sympathetic and parasympathetic systems via vagus nerve and intermediolateral column of the medulla. The response is, usually, the release of noradrenaline, which controls blood pressure and, consequently, cardiovascular function.[40]

Thus, cardiovascular autonomic dysfunction in PD can be characterized by preganglionic (baroreflex failure) and postganglionic (sympathetic denervation) lesions, causing cardiovascular adversities, such as: neurogenic orthostatic hypotension, supine hypertension and postprandial hypotension.[3]

2.1 Orthostatic Hypotension

Orthostatic hypotension (OH) is defined, by consensus, as a sustained drop in systolic blood pressure (BP) >20mmHg or diastolic BP >10mmHg over a time interval of 3 minutes standing or greater head-up tilt during formal tilt table testing.[41] The International Parkinson and the Movement Disorder Society has added neurogenic and symptomatic OH as a prodromal criterion for PD.[42] This is likely because OH is the most common autonomic symptom in PD, with a reported prevalence ranging from 9.6% to 64.9%.[43] Furthermore, the first expression of OH may be during the onset of the disease.[44] Thus, neurogenic OH can be expressed through various symptoms, such as dizziness when standing, visual disturbances, headache and difficulty breathing; which can lead to an increased risk of falls.[45]

OH can also be manifested by non-neurogenic factors such as medicines (diuretic and vasodilators), hypovolemia and heart failure. However, neurogenic OH is manifested in PD due to inadequate neurocirculatory responses to postural change caused by baroreflex-cardiovagal failure and impaired release of norepinephrine.[46] Fundamentally, this last-mentioned factor is directly related to the loss of peripheral and postganglionic sympathetic fibers involved in cardiac innervation, which can cause OH neurogenic as a result of lower noradrenaline concentrations in PD patients.[47] In this context, the reduction of this neurotransmitter may be associated with the involvement of the locus coeruleus due to Lewy body progression, since it is the primary source of norepinephrine production in the brain.[3]

Thus, analyzing the causes of neurogenic OH of baroreflex-cardiovagal failure and impaired norepinephrine release, it becomes evident that the onset of orthostatic hypotension may be associated with Braak stage 2. This conclusion corroborates the progression of Lewy bodies to central structures, once that there is involvement of bulbar structures (vagus) and pontine structures (locus coeruleus). This rationale is supported by previous reports of a possible noradrenergic depletion in the locus coeruleus, given that it is only from Braak stage 2 onward that both the involvement of the vagus nerve (already affected in stage 1 and associated with cardiovagal failure) and the compromise of the locus coeruleus, linked to noradrenergic depletion, are observed.

2.2 Supine hypertension

Supine hypertension (SH) is defined as a systolic BP ≥150 mmHg and the diastolic BP ≥90 mmHg when in the supine position. In PD, SH may be manifested along with OH.[48] The prevalence of SH in PD is 34%.[7]

In this sense, the pathophysiology of SH in PD remains unknown. However, it is recognized that it may be mediated by an increase in peripheral vascular resistance due to residual sympathetic tone. Furthermore, impaired cardiovagal baroreflex function has also been associated with SH in PD.[48]

Thus, due to the fact that there is no elucidation regarding its pathophysiology, it will not be possible to accurately determine the beginning of its progression in PD. Therefore, given the association of SH with baroreflex-cardiovagal involvement and that it may be expressed together with OH, it is assumed that its onset is related to Braak stage 2.

2.3 Postprandial Hypotension

Postprandial hypotension (PPH) is defined as a drop of ≥20mmHg in systolic BP within two hours of eating.[49] It occurs in the early stages of PD and has a prevalence of approximately 30%. Furthermore, PPH is more common in Parkinson's patients with orthostatic hypotension.[50]

Physiologically, after food intake there is an increase in splanchnic blood flow, causing a decrease in venous return and, consequently, a reduction in cardiac output. However, in patients with PD who have sympathetic dysfunction, there is no adequate increase in peripheral vascular resistance to try to compensate for this mechanism of reduced cardiac output, leading, as a result, to PPH.[49] As reported with orthostatic hypotension, the association between depletion of sympathetic fibers and involvement of the cardiovagal baroreflex is also involved in PPH.[51]

Thus, the involvement of peripheral and postganglionic sympathetic fibers involved in cardiac innervation may, as in orthostatic hypotension, contribute to reductions in norepinephrine concentrations. In this sense, although it was not possible to find a report on the association of the locus coeruleus with PPH, it is inferred that norepinephrine reductions may be involved in the progression of Lewy bodies to the pontine regions, since the main source of this neurotransmitter is in the locus coeruleus. Accordingly, it can be inferred that the onset of postprandial hypotension may be associated with Braak stage 2, based on the reasoning presented.

3. Urogenital Dysfunctions

Fundamentally, causes related to the urogenital system are categorized as urinary and sexual dysfunction. Urinary dysfunction is primarily caused by central mechanisms in PD, affecting bladder storage and emptying functions. Sexual dysfunction is characterized by reduced libido and sexual arousal, which are regulated by neurobiological, endocrinological and psychological mechanisms.[7]

In this sense, urinary dysfunction is basically focused on changes in the bladder, with its main symptoms being nocturia, increased frequency and urinary incontinence.[52] The sensation of incomplete bladder emptying is more related to other urological causes, drug induction or other neurodegenerative diseases.[53]

Thus, sexual dysfunction in men is more related to erectile dysfunction and premature ejaculation, while in women there is a predominance of loss of lubrication.[53]

3.1 Urinary Dysfunction

Contrary to what was presented in OH, a seven-year longitudinal study revealed that urinary dysfunction was the most common autonomic symptom in patients with PD, affecting approximately 95% to 97% of these patients.[54] Of the lower urinary tract symptoms, the most prevalent is nocturia, followed by increased frequency and urinary incontinence.[55]

Bladder storage is dependent on the sacral autonomic reflex. This reflex is believed to be facilitated primarily by the pontine micturition center (PMC), which is located adjacent to the locus coeruleus. Regarding bladder emptying, it is assumed that it is dependent on the

autonomic spino-bulbo-spinal reflex, which involves the midbrain periaqueductal gray matter (PAG) and the PMC.[52]

Physiologically, the micturition reflex is related to the frontal-basal ganglia D1 dopaminergic circuit. The basal ganglia part of this circuit can be explained by neuronal firing of the compact part of the substantia nigra, which appears to activate the direct dopamine D1-GABAergic pathway. Thus, D1 (inhibitory) inhibits the voiding reflex both through the basal ganglia output nuclei and through GABAergic collateral pathways (particularly the PAG). In contrast to the basal ganglia, the relationship of the frontal cortex in this circuit can be explained by the fact that it is considered the superior center of urination, as lesions in it produce hyperactivity of the detrusor muscle of the bladder.[56]

In this context, the frontal-basal ganglia D1 dopaminergic circuit is compromised in PD, resulting in disinhibition of the micturition reflex and, consequently, in overactivity of the bladder detrusor muscle and symptoms of overactive bladder.[56] Such involvement of this circuit may be related to the progression of Lewy bodies to central structures, such as the basal ganglia and frontal cortex.

Thus, following the proposed reasoning, the onset of dopaminergic involvement in the basal ganglia in PD may only be expressed from Braak stage 3 onwards; while involvement of the frontal cortex may only be manifested in more advanced stages of the disease. In this sense, it is possible to infer that symptoms related to urinary dysfunction may be initially associated with Braak stage 3 due to involvement of the dopaminergic circuit in the basal ganglia.

3.2 Sexual Dysfunction

Sexual dysfunction is an extremely negative influence on the quality of life and mood of patients with PD, which can be expressed in both men and women.[7] The prevalence of sexual symptoms in patients with PD ranges from 37% to 65%.[57] In a study of 1072 PD patients, erectile dysfunction and premature ejaculation were the most common symptoms in men. In women, the most common were vaginal tightness and loss of lubrication. A decrease in libido was reported for both sexes.[57]

Under physiological conditions, penile erection can be classified as reflex or psychogenic. Reflex erection occurs due to genital stimulation via the sensory fiber pathway of the dorsal penile nerve to segments S2-S4 of the spinal cord. From the medulla, synaptic connections extend to the parasympathetic cavernous nerve of the penis, resulting in vasodilation of the penile arteries. Regarding psychogenic erection, it occurs in response to visual/erogenous stimuli that connect the brain to peripheral nerve structures, such as the inferior hypogastric nerve and the pelvic plexus.[53]

Thus, sexual dysfunction in PD is not well understood.[52] The aforementioned peripheral nerve structures themselves have rarely been studied in the context of PD.[7] However, it is known that most patients with PD manifest the onset of sexual dysfunction only after the appearance of motor disorders.[52] From this reasoning, it is deduced that the onset of symptoms related to sexual dysfunction will only occur from Braak stage 3 onwards. This conclusion is based on the fact that parkinsonian motor symptoms can be expressed through the involvement of mesencephalic structures, which are only involved from stage 3 onwards.

4. Thermoregulatory Dysfunction

Central and peripheral mechanisms are used to maintain internal body temperature around 37°C. The anterior and preoptic hypothalamic areas act as the main thermosensitive regions at the central level through their heat-sensitive neurons. Thus, the pathways for the hypothalamic response for heat loss or conservation involve projections to the rostral raphe pallidus area in the medulla. Following this reasoning, the raphe pallidus projects to sympathetic and motor neurons in the spinal cord which then activate peripheral effectors, such as skin vasomotor tone, shivering and metabolic thermogenesis. In addition to the CNS, peripheral thermoregulation is mediated predominantly by the sympathetic nervous system, which uses norepinephrine to promote vasoconstriction and acetylcholine to stimulate sweat glands.[58]

In this sense, the thermoregulatory disorders caused by PD are mediated by failures at central and peripheral levels. At the central level, hypothalamic involvement by Lewy bodies has been demonstrated.[58] At the peripheral level, it was reported that sudomotor and sympathetic vasoconstrictor functions are impaired due to a reduction in the density of intraepidermal nerve fibers and an increase in α-synuclein deposition in the skin.[59] Such conditions may be evidenced by biopsy findings showing clusters of cutaneous nerve fibers, hyperinnervation in the upper dermis and increased branching of intraepidermal nerve fibers.[60]

Thermoregulatory dysfunction, essentially hyperhidrosis, is one of the most common characteristics of body temperature regulation disorders in PD. It is observed in around 30% to 50% of these patients. It is commonly reported as being episodic; however, it can be generalized, affecting the entire body or asymmetrically. If asymmetrical, the condition tends to affect the side with the greatest motor deficit. Furthermore, episodes of hyperhidrosis in Parkinson's patients with hypotension are more likely to occur after meals or at night.[58]

Thus, from an imaging study, it was possible to deduce that thermoregulatory disorders in PD may be related to involvement of the hypothalamus. This fact is based on the deposition of α-synuclein in this region, causing a reduction in functional connectivity with other regions of the brain and, consequently, in the dysregulation of the ANS.[61] In this sense, this loss of hypothalamic connection may be related to the formation of small- and

large-fiber peripheral neuropathy in PD. This condition may occur due to reduced autonomic innervation of blood vessels and sweat glands. However, it is worth noting that this condition, although observed early in the disease, becomes more prominent only in more advanced stages.[58]

In this context, following Braak's theory, thermoregulatory dysfunctions may initially be related to Braak stage 3. This conclusion may be explained by the previously proposed analysis suggesting that the loss of hypothalamic connections can indirectly affect various peripheral structures, such as sweat glands and sympathetically influenced nerve fibers, leading to thermoregulatory dysfunctions, including hyperhidrosis.

In this way, it is worth mentioning that, although Braak stages can contribute to the identification of Lewy bodies in both central and peripheral structures in PD, its application in clinical practice presents limitations, such as the requirement for invasive histopathological analysis and the inherent clinical heterogeneity of the disease. Therefore, the application of Braak stages may be inaccurate in specific genetic forms or phenotypic variants of PD that are not associated with Lewy body pathology. In such cases, alternative approaches, such as the use of peripheral biomarkers and molecular imaging, may offer valuable insights into the pathological progression of the disease.

Thus, evaluating this important relationship between Braak stages and the initial recognition of dysautonomias in PD, Figure 4 was created. This figure demonstrates a possible initial association between the analyzed dysautonomias and their respective Braak stages.

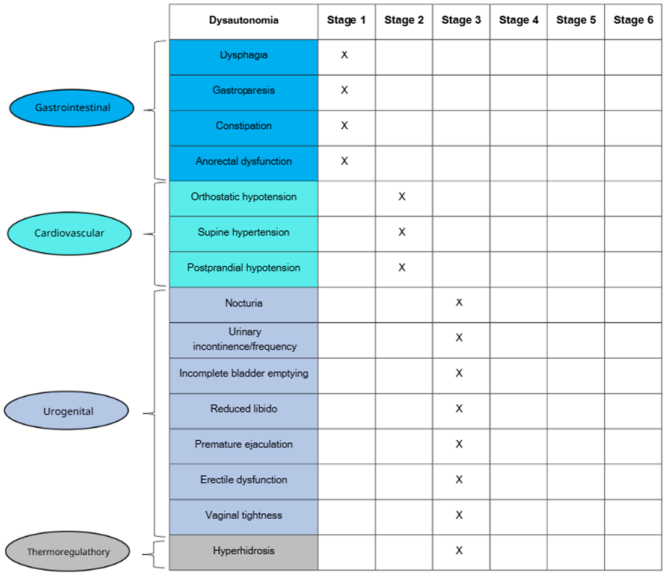

Figure 4 - The possible association between the initial manifestations of dysautonomias and the Braak stages in Parkinson's disease

In this sense, from the analysis of this figure, it is possible to observe a probable pattern of initial presentation of dysautonomias in PD. This pattern can be explained by analyzing the initial expressions of dysautonomias, since they appear to be evident even before the emergence of classic motor symptoms. Thus, it is worth mentioning that, although dysautonomias tend to be expressed in the early stages of the disease, the worsening of dysautonomic symptoms reinforces the fact that autonomic dysfunction is directly associated with the duration and severity of PD. Furthermore, involvement of central and peripheral structures suggests the involvement of multiple organs, which requires individualized and adequate management from the early stages of the disease.

In this context, the same seven-year longitudinal study carried out to determine the percentage of Parkinson's patients affected by urogenital dysfunction reported that the percentage of patients with multiple autonomic symptoms increased even further over the 7-year follow-up. Furthermore, all participants reported at least one autonomic symptom at the last study follow-up.[54] In this way, it is worth emphasizing that therapeutic strategies targeting dysautonomic manifestations, such as the use of dopaminergic agonists and dopamine precursors, may either alleviate or worsen these symptoms, underscoring the need for individualized treatment to each patient.[11]

CONCLUSION

Thus, autonomic dysfunctions are non-motor symptoms that are frequently present in PD. ANS dysregulation contributes to a significant impairment in the quality of life of patients who suffer from PD. Early diagnosis of dysautonomias is of paramount importance for the elucidation of PD, since dysautonomic disorders can precede classic motor symptoms years before their manifestation. Furthermore, the application of Braak neuropathological stages to identify the involvement of central and peripheral structures suggests great value in recognizing the pathological progression of Lewy bodies in PD.

On the whole, the early recognition of dysautonomia in PD can be highly relevant, contributing not only to a more accurate diagnosis, but also to timely therapeutic interventions. The identification of symptoms, such as constipation, orthostatic hypotension and urinary dysfunction, may enable treatment even before the onset of motor symptoms, potentially preventing complications and supporting more effective and individualized disease management.

REFERENCES

1. Rosso AL, Nicaretta DH, de Mattos JP. Correlações anatomoclínicas na doença de Parkinson. Rev Bra de Neuro. 2008 Jan 1;41-47.
2. Greenland JC, Barker RA. The Differential Diagnosis of Parkinson's Disease. Stoker TB, Greenland JC, editors. PubMed. Brisbane (AU): Codon Publications; 2018. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch6.
3. Goldstein DS. Dysautonomia in Parkinson's disease: neurocardiological abnormalities. The Lancet Neuro. 2003 Nov;2(11):669–76. https://doi.org/10.1016/S1474-4422(03)00555-6.
4. Pfeiffer RF. Autonomic Dysfunction in Parkinson's Disease. Neurotherapeutics. 2020 Oct; 17(4):1464-1479. https://doi.org/10.1007/s13311-020-00897-4.
5. Jon Stoessl A. Prevention and Management of Late Stage Complications in Parkinson's Disease. Cana J of Neuro Sci. 1992;19(1):113-116. https://doi.org/10.1017/S0317167100041470.
6. Pfeifer MA, Weinberg CR, Cook D, Best JD, Reenan A, Halter JB. Differential changes of autonomic nervous system function with age in man. The Ameri J of Med. 1983 Aug;75(2):249-258. https://doi.org/10.1016/0002-9343(83)91201-9.
7. Chen Z, Li G, Liu J. Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. Neuro of Disea. 2020 Feb 1;134:104700. https://doi.org/10.1016/j.nbd.2019.104700.
8. Sun R, Guo Y. Gene signatures and immune correlations in Parkinson's disease Braak stages. Euro J of Med Resea. 2025 Apr 15;30(1). https://doi.org/10.1186/s40001-025-02554-y.
9. Kaufmann H. Disautonomías más comunes. Rev de Neuro. 2003;36(01):93-96.
10. Banwinkler M, Dzialas V, Hoenig MC, Thilo van Eimeren. Gray Matter Volume Loss in Proposed Brain-First and Body-First Parkinson's Disease Subtypes. Move Disor. 2022 Aug 9;37(10):2066–74. https://doi.org/10.1002/mds.29172.
11. Nicaretta DH, Rosso AL, de Mattos JP. Dysautonomy in Parkinson's disease. Review of the literature. Rev Bra de Neuro. 2011 Jan 1; 47(4):25-29.
12. Greenamyre JT. Advances in Neurology, vol 53, Parkinson's Disease: Anatomy, Pathology, and Therapy. Arch of neuro. 1991 Sep 1;48(9):897–907. https://doi.org/10.1001/archneur.1991.00530210023004.
13. Braak H, Tredici KD, Rüb U, de Vos RAI, Jansen Steur ENH, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neuro of Agi. 2003 Mar;24(2):197–211. https://doi.org/10.1016/S0197-4580(02)00065-9.
14. Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. Nat Rev Neuro. 2017 Jun 8;18(7):435–50. https://doi.org/10.1038/nrn.2017.62.
15. Portal Regional da BVS [Internet]. 2018. Available from: https://bvsalud.org/. Access: 03/03/2026.
16. Wolters EC, Braak H. Parkinson's disease: premotor clinico-pathological correlations. J of Neu Transm Supple. 2006;(70):309–19. https://doi.org/10.1007/978-3-211-45295-0_47.
17. Abbott RD, Petrovitch H, White LR, Masaki KH, Tanner CM, Curb JD, et al. Frequency of bowel movements and the future risk of Parkinson's disease. Neuro. 2001 Aug 14;57(3):456–62. https://doi.org/10.1212/WNL.57.3.45.
18. Sender Herschorn, Jung Wan Koo, Sun Ok Song, Kwang Wook Jo, Moon Ho Lee, Jang W. Central cholinergic dysfunction could be associated with oropharyngeal dysphagia in early Parkinson's disease. J Neural Transm. 2015 Jul 22;122(11):1553–61. https://doi.org/10.1007/s00702-015-1427-z.
19. Hawkes CH, Shephard BC, Daniel SE. Olfactory dysfunction in Parkinson's disease. J of Neuro, Neurosu & Psychi. 1997 May 1;62(5):436–46. https://doi.org/10.1136/jnnp.62.5.436.
20. Friedman JH, Millman RP. Sleep Disturbances and Parkinson's Disease. CNS Spectrums. 2008 Mar;13(S4):12–7. https://doi.org/10.1017/S1092852900017272.
21. Olson EJ, Boeve BF, Silber MH. Rapid eye movement sleep behaviour disorder: demographic, clinical and laboratory findings in 93 cases. Brain. 2000 Feb 1;123(2):331–9. https://doi.org/10.1093/brain/123.2.331.
22. Snider SR, Fahn S, Isgreen WP, Cote LJ. Primary sensory symptoms in parkinsonism. Neuro. 1976 May 1;26(5):423–433. https://doi.org/10.1212/WNL.26.5.423.
23. Tousi B. Diagnosis and Management of Cognitive and Behavioral Changes in Dementia With Lewy Bodies. Curr Treat Opt in Neuro. 2017 Oct 9;19(11). https://doi.org/10.1007/s11940-017-0478-x.
24. Pelz JO, Belau E, Fricke C, Classen J, Weise D. Axonal Degeneration of the Vagus Nerve in Parkinson's Disease—A High-Resolution Ultrasound Study. Front in Neuro. 2018 Nov 12;19.https://doi.org/10.3389/fneur.2018.00951.
25. Takizawa C, Gemmell E, Kenworthy J, Speyer R. A Systematic Review of the Prevalence of Oropharyngeal Dysphagia in Stroke, Parkinson's Disease, Alzheimer's Disease, Head Injury, and Pneumonia. Dysphagia. 2016 Mar 12;31(3):434-441. https://doi.org/10.1007/s00455-016-9695-9.
26. Ali G, Wallace K, Schwartz R, DeCarle D, Zagami A, Cook I. Mechanisms of oral-pharyngeal dysphagia in patients with Parkinson's disease. Gastroenterology. 1996 Feb;110(2):383-392. https://doi.org/10.1053/gast.1996.v110.pm8566584.
27. Jurkiewicz AL, Marques JM, Santos RS, Marcelino PCO, Herrero F, Gasparim AZ. Deglutition and Cough in Different Degrees of Parkinson Disease. Arqui Inter de Otorrino. 2011 Apr;15(02):181-188. https://doi.org/10.1590/S1809-48722011000200010.
28. Denis Michael Rudisch, Krasko MN, Burdick R, Broadfoot CK, Rogus-Pulia N, Ciucci MR. Dysphagia in Parkinson Disease: Part I – Pathophysiology and Diagnostic Practices. Curr Phys Med Rehabil Rep. 2023 Mar 28;11(2):176–87. https://doi.org/10.1007/s40141-023-00392-9.
29. Heetun ZS, Quigley EMM. Gastroparesis and Parkinson's disease: A systematic review. Parkin & Rela Disor. 2012 Jun;18(5):433–40. https://doi.org/10.1016/j.parkreldis.2011.12.004.
30. Marrinan S, Emmanuel AV, Burn DJ. Delayed gastric emptying in Parkinson's disease. Move Disor. 2013 Oct 21;29(1):23–32. https://doi.org/10.1002/mds.25708.
31. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, et al. Bowel Disorders. Gastroenterology. 2016 May;150(6):1393-1407. http://dx.doi.org/10.1053/j.gastro.2016.02.031.
32. Malek N, Lawton MA, Grosset KA, Bajaj N, Barker RA, Burn DJ, et al. Autonomic Dysfunction in Early Parkinson's Disease: Results from the United Kingdom Tracking Parkinson's Study. Move Disor Clin Prac. 2016 Nov 24;4(4):509–16. https://doi.org/10.1002/mdc3.12454.
33. Ueki A, Otsuka M. Lifestyle risks of Parkinson's disease: Association between decreased water intake and constipation. J of Neuro. 2004 Oct;251(S7):18–23. https://doi.org/10.1007/s00415-004-1706-3.
34. Berg D, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, et al. MDS research criteria for prodromal Parkinson's disease. Move Disor. 2015 Oct;30(12):1600-1611.https://doi.org/10.1002/mds.26431.
35. Braak H, de Vos RAI, Bohl J, Del Tredici K. Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach' s plexuses in cases staged for Parkinson's disease-related brain pathology. Neuros Lette. 2006 Mar;396(1):67–72. https://doi.org/10.1016/j.neulet.2005.11.012.
36. Lebouvier T, Neunlist M, Bruley des Varannes S, Coron E, Drouard A, N'Guyen JM, et al. Colonic Biopsies to Assess the Neuropathology of Parkinson's Disease and Its Relationship with Symptoms. Cookson MR, editor. PLoS ONE. 2010 Sep 14;5(9). https://doi.org/10.1371/journal.pone.0012728.
37. Yao L, Liang W, Chen J, Wang Q, Huang X. Constipation in Parkinson's Disease: A Systematic Review and Meta-Analysis. Euro Neuro. 2022 Dec 5;86(1):34–44. https://doi.org/10.1159/000527513.

38. Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease. Current Treatment Options in Neuro. 2018 Oct 25;20(12). https://doi.org/10.1007/s11940-018-0539-9.
39. Sung HY, Choi MG, Kim YI, Lee KS, Kim JS. Anorectal manometric dysfunctions in newly diagnosed, early-stage Parkinson's disease. J of Clin Neuro. 2012 Sep;8(3):184–9. http://dx.doi.org/10.3988/jcn.2012.8.3.184.
40. Lima CFS, Ferraz HB, Andrade LAF de. Disautonomia na Doença de Parkinson. Rev Neuro. 1999 Oct 31;5(3):53-58.
41. Palma JA, Kaufmann H. Orthostatic Hypotension in Parkinson Disease. Clin in Geri Med. 2020 Feb;36(1):53–67. https://doi.org/10.1016/j.cger.2019.09.002.
42. Heinzel S, Berg D, Gasser T, Chen H, Yao C, Postuma RB. Update of the MDS research criteria for prodromal Parkinson's disease. Move Disor. 2019 Aug 14;34(10):1464–70. https://doi.org/10.1002/mds.27802.
43. Zeng J, Xing Y, Mei S, Xu B, Xue X, Song H, et al. The differences of orthostatic hypotension in patients with Parkinson's disease and multiple system atrophy. Front in Neuro. 2023 Jan 26;14. https://doi.org/10.3389/fneur.2023.1070943.
44. Kim JS, Lee SH, Oh YS, Park JW, An JY, Park SK, et al. Cardiovascular Autonomic Dysfunction in Mild and Advanced Parkinson's Disease. J of Move Disor. 2016 May 25;9(2):97–103. https://doi.org/10.14802/jmd.16001.
45. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RMA. Prevalence of orthostatic hypotension in Parkinson's disease: A systematic review and meta-analysis. Parkin & Rela Disor. 2011 Dec;17(10):724–9. https://doi.org/10.1016/j.parkreldis.2011.04.016.
46. Cutsforth-Gregory JK, Low PA. Neurogenic Orthostatic Hypotension in Parkinson Disease: A Primer. Neuro and Thera. 2019 Aug 27;8(2):307–24. https://doi.org/10.1007/s40120-019-00152-9.
47. Oka H, Yoshioka M, Onouchi K, Morita M, Mochio S, Suzuki M, et al. Retracted: Characteristics of orthostatic hypotension in Parkinson's disease. Brain. 2007 Sep 1;130(9):2425-2432. https://doi.org/10.1159/000073865.
48. Zhu S, Li H, Xu X, Luo Y, Deng B, Guo X, et al. The Pathogenesis and Treatment of Cardiovascular Autonomic Dysfunction in Parkinson's Disease: What We Know and Where to Go. Agi and Disea. 2021;12(7):1675. https://doi.org/10.14336/AD.2021.0214.
49. Grosu C, Noea O, Maştaleru A, Ignat EB, Leon MM. Neurogenic Orthostatic Hypotension in Parkinson Disease-A Narrative Review of Diagnosis and Management. J of Clin Med. 2025 Jan 19;14(2):630. https://doi.org/10.3390/jcm14020630.
50. Yalcin A, Atmis V, Karaarslan Cengiz O, Cinar E, Aras S, Varli M, et al. Evaluation of Cardiac Autonomic Functions in Older Parkinson's Disease Patients: a Cross-Sectional Study. Agi and Disea. 2016;7(1):28. https://doi.org/10.14336/AD.2015.0819.
51. Umehara T, Toyoda C, Oka H. Postprandial hypotension in de novo Parkinson's disease: A comparison with orthostatic hypotension. Parkin & Rela Disor. 2014 Jun;20(6):573–7. http://dx.doi.org/10.1016/j.parkreldis.2014.02.007.
52. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. Genitourinary dysfunction in Parkinson's disease. Move Disor. 2010 Jan 13;25(1):2–12. https://doi.org/10.1002/mds.22519.
53. Margolesky J, Betté S, Singer C. Management of Urologic and Sexual Dysfunction in Parkinson Disease. Clin in Geri Med. 2020 Feb;36(1):69–80. https://doi.org/10.1016/j.cger.2019.09.011.
54. Stewart CB, Ledingham D, Foster VK, Anderson KM, Sahana Sathyanarayana, Galley D, et al. The longitudinal progression of autonomic dysfunction in Parkinson's disease: A 7-year study. Front in Neuro. 2023 Apr 12;14. https://doi.org/10.3389/fneur.2023.1155669.
55. Campos-Sousa RN, Quagliato E, da Silva BB, de Carvalho RM, Ribeiro SC, de Carvalho DFM. Urinary symptoms in Parkinson 's disease: prevalence and associated factors. Arqui de Neuro-Psi. 2003 Jun 1;61(2B):359–63. https://doi.org/10.1590/S0004-282X2003000300007.
56. Sakakibara R, Tateno F, Nagao T, Yamamoto T, Uchiyama T, Yamanishi T, et al. Bladder function of patients with Parkinson's disease. Inter J of Uro. 2014 Feb 27;21(7):638–46. https://doi.org/10.1111/iju.12421.
57. Truong DD, Bhidayasiri R, Wolters E. Management of non-motor symptoms in advanced Parkinson disease. J of the Neuro Sci. 2008 Mar;266(1-2):216–28. https://doi.org/10.1016/j.jns.2007.08.015.
58. Coon EA, Low PA. Thermoregulation in Parkinson disease. Thermoregulation: From Basic Neuroscience to Clinical Neurology, Part II. 2018;715–25. https://doi.org/10.1016/B978-0-444-64074-1.00043-4.
59. A. Kuzkina, L. Schulmeyer, C.-M. Monoranu, Volkmann J, Sommer C, Doppler K. The aggregation state of α-synuclein deposits in dermal nerve fibers of patients with Parkinson's disease resembles that in the brain. Parkin & Rela Disor. 2019 Jul 1;64:66-72. https://doi.org/10.1016/j.parkreldis.2019.03.003.
60. Nolano M, Caporaso G, Manganelli F, Stancanelli A, Borreca I, Mozzillo S, et al. Phosphorylated α-Synuclein Deposits in Cutaneous Nerves of Early Parkinsonism. J of Parkin Disea. 2022 Dec 16;12(8):2453–68. https://doi.org/10.3233/JPD-223421.
61. Seo K, Oyama G, Yamamoto T. Subregional analysis of the amygdala, thalamus, and hypothalamus at the pre-decline stage in Parkinson's disease with later cognitive impairment. Front in Agi Neuro. 2025 May 9;17. https://doi.org/10.3389/fnagi.2025.1588027.