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Review

Non-Motor Features of Parkinson Disease: A New Clinical State of The Art

Isadora Vergamini Lamana [1, #], Ana Carolina Gomes de Oliveira [1, #], Larissa Tarraf Bertazzo [1], Natália Balbo Arantes Nogueira [1], Júlio César Claudino dos Santos [2, 3, *], Luana Stangherlin [3]

[1] Barão de Mauá University Center (CBM), Ribeirão Preto, São Paulo, Brazil.
[2] Federal University of Ceará (UFC), Fortaleza, Ceará, Brazil.
[3] Unifacvest University Center (UNIFACVEST), Lages, Santa Catarina, Brazil.

*An equal contribution of these two authors.
* Correspondence: julio.santos@alu.ufc.br.

Abstract: Parkinson's disease (PD) is a multisystemic, progressive disorder in which there is dopaminergic neuronal degeneration, with involvement of the substantia nigra and consequently the development of pre-motor, non-motor and motor symptoms, leading to a difficulty in the patient's quality of life. The aim of this study was to carry out a narrative review of the literature to update the state of the art on the non-motor symptoms of PD. A review of the literature from the last 10 years was carried out, highlighting mainly the prodromal manifestations of PD, such as sleep symptoms, sensory symptoms, neuropsychiatric and autonomic symptoms in their prodromal phases and their relationship with motor symptoms. Thus, we reiterate that premotor manifestations precede motor symptoms by up to 20 years and, consequently, the diagnosis of this neurodegenerative disease with a guarded prognosis. Thus, more longitudinal studies are needed looking at the prodromal symptoms of PD to gain a broad understanding and consequent early diagnosis of the disease, in order to provide biomarkers and support for early treatment with an improved prognosis for individuals living with this neurodegenerative condition.

Keywords: Parkinson's Disease; Non-Motor Symptoms; Pre-Motor Symptoms; Prodromes.

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1. Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative pathology, with an unknown etiology, which stems from progressive and insidious dopaminergic neuronal degeneration in the substantia nigra, characterizing its classic symptoms: bradykinesia, rigidity, postural instability and resting tremor. In addition to motor manifestations, as part of the commemoratives of PD, many non-motor symptoms may be present, such as olfactory dysfunction, sleep problems, constipation, autonomic disorders, depression, anxiety [1-5].

Given the relevance of the aforementioned information, epidemiological studies have shown that, with approximately one diagnosis per hour, this pathology has a global prevalence of 200/100,000 individuals. In addition, the incidence increases 5 to 10 times from the sixth to the ninth decade of life, leading to an increase ranging from 5/100,000 to more than 35/100,000 new cases, with an estimated doubling of diagnoses by 2040. It is worth noting the significant morbidity and mortality presented, in which the majority of patients die due to complications from this disease. From its onset, the pathology develops progressively and continuously, showing itself in 3 phases, the preclinical, pro-

dromal and clinical, which are respectively the asymptomatic onset of neurodegeneration, non-motor symptoms and motor symptoms [3, 6, 7].

Still in this context, non-motor manifestations (NMS) are a set of appearances that can arise even before motor alterations that significantly compromise patients' quality of life [8], containing psychiatric symptoms, urinary and sexual dysfunctions, gastrointestinal problems, sensory impairments, circadian cycle disorders, hyposmia, unintentional weight loss, osteosarcopenia, among other disorders [9, 10]. It should be noted that almost all patients mentioned the presence of NMS, with psychiatric symptoms being the most prevalent [6]. In addition, as they are considered pathological changes intrinsic to the pathophysiology of PD, these conditions can also manifest themselves due to adverse effects induced by drug therapy, of genetic, dopaminergic or non-dopaminergic origin [9, 11].

Over the last few decades, the pharmacological and surgical therapy developed for the disease's motor symptoms has been based on strategies to replace dopamine, but due to non-specific symptoms, the management of NMS is still restricted. Although the diagnosis of PD is based on the clinical effects of the deficiency of this neurotransmitter, motor symptoms appear when approximately 70% of the dopaminergic system is already compromised, which makes it essential to identify patients with the potential to progress and develop this neurodegenerative disease, since it is estimated that non-motor symptoms appear in at least a third of PD patients. Interestingly, olfactory deficits, rapid eye movement sleep behavior disorder (RBD), fatigue and depression can contribute as markers in the preclinical stages of PD [7, 12]. Therefore, in line with the aforementioned information and giving significant importance to the non-specific manifestations presented in the condition, the aim of this study is to explore the relationship between prodromal, pre-motor and non-motor symptoms presented in Parkinson's disease.

2. Method

A narrative literature review was executed in the medline database (pubmed), from 2014 to 2024 about the role of non-motor features of Parkinson disease. In the medline database (PubMed), 221 articles were found through the mesh descriptor "(((parkinson disease[text word]) and (parkinson disease[title/abstract])) and (signs[title/abstract] and symptoms[title/abstract])) and (signs[text word] and symptoms[text word])" of which 117 were included, after the exclusion of articles following the first set of criteria - exclusion of titles that did not address the role of non-motor features of Parkinson disease, articles not included in the research period of 2014-2024, as well as articles that were not originally in english. After this phase, a second set of criteria was applied - exclusion of the abstracts that did not address the role of non-motor features of Parkinson disease, which led to the exclusion of 209 articles. After the selection, 7 new articles were manually selected and added, according to their relevance to the study. finally, aiming to enrich the discussion, 32 articles originally in English were manually selected and added according to their relevance in the synthesis of qualitative evidence.

3. Results and Discussion

In view of the numerous cases of diagnosis of PD, most of which occur after the appearance of the classic motor symptoms, it is essential to discuss the prodromes and non-motor symptoms concomitant with this disease. Thus, through a review of the current literature, the presence of sensory symptoms (hyposmia, pain, visual disturbance and taste dysfunction), sleep symptoms (insomnia, restless legs syndrome, REM sleep behavior disorders), neuropsychiatric symptoms (cognitive dysfunction, psychosis, language dysfunction, anxiety, depression) and autonomic symptoms (dysphagia, urinary dysfunction, sexual dysfunction, gastrointestinal tract disorder) are among the many early diagnoses that contribute to the investigation of this disease in its clinical progression (Figure 1 and Table 1).

Figure 1. Symptoms of Parkinson disease.

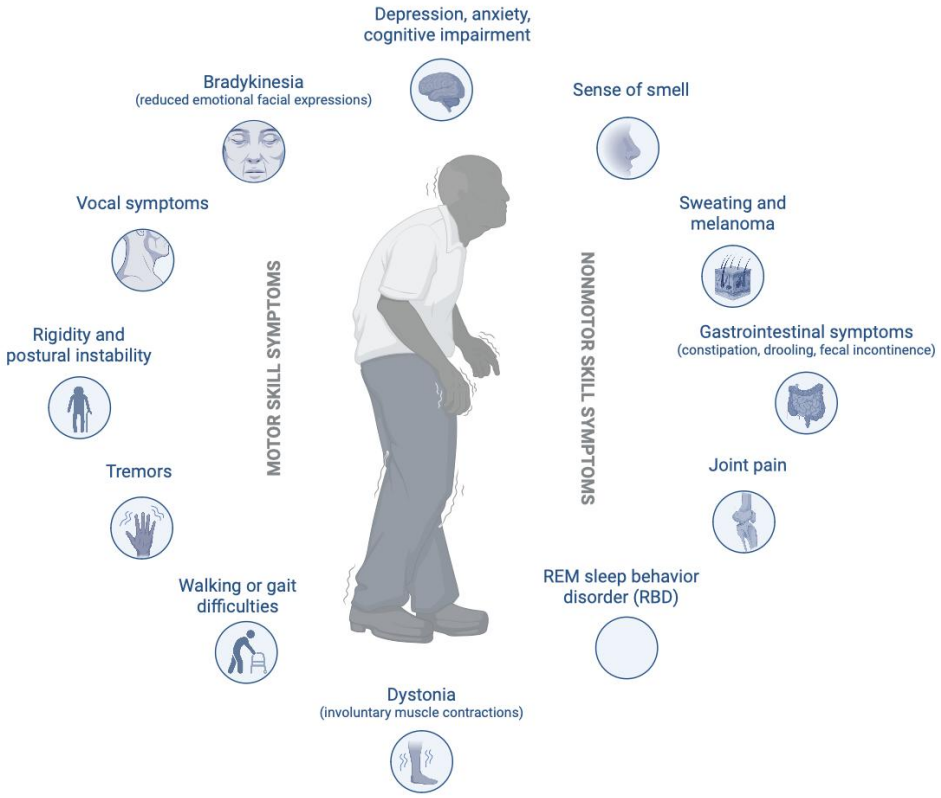

Table 1. Summary description of non-motor symptom studies.

References	Study Type	Non-Motor Symptoms	Definition
[13]	Review	Hyposmia	Reduced ability to sense and detect odors is a highly prevalent symptom in patients and may precede the appearance of motor characteristics by several years.
[16]	Review	Pain	A very common non-motor symptom with a prevalence of between 40 and 85%, increasing progressively as the disease progresses. It can be classified into five types: radicular or neuropathic pain, musculoskeletal pain, dystonia-related pain, acatitic discomfort and primary or central parkinsonian pain.
[19]	Review	Visual Disturbance	The appearance of manifest visual complaints in 70% of PD cases, including visual disturbance, decreased sensitivity, and impaired color discrimination.
[21]	Review	Gustatory Dysfunction	Gustatory function impairment has been elucidated, though with less emphasis and perception due to its reduced impact on patients daily lives.
[23]	Review	Insomnia	Being a subjective symptom, it is a frequent complaint, with 60% reporting sleep problems and 76% stating they experience poor sleep quality.

[27]	Review	Restless Legs Syndrome	Despite the difficulty in diagnosis due to multiple similar factors, the prevalence of Restless Legs Syndrome (RLS) was 15.74%, with an association between dopaminergic dysfunction in PD and RLS.
[26]	Case-Control	REM Sleep Behavior Disorder	Considering parasomnia disorder, patients exhibit episodic undesirable behaviors occurring at sleep onset, during sleep, or upon awakening.
[30]	Narrative Review	Cognitive Dysfunction	As one of the most prevalent non-motor symptoms, cognitive dysfunction presents in 20-33% of cases with mild cognitive impairment (MCI); more than 40% of patients develop MCI within six years of diagnosis, and 60-80% progress to dementia in PD.
[33]	Review	Psychosis	With an estimated prevalence of 43-63% in the more advanced stages of the disease, psychosis shows a progressive increase over time. It is noteworthy that the pattern of psychotic symptoms in PD differs from that of other psychotic disorders.
[36]	Case-Control	Language Dysfunction	Language dysfunction in patients involves word impairment, increased frequency of grammatical errors, and difficulties in interpreting figurative language and semantic ambiguities.
[39]	Review	Anxiety	The impact on patients' quality of life is significant, as the interaction between motor symptoms and anxiety results in a vicious cycle. The prevalence rate of certain manifestations is between 20-46%.
[41]	Review	Depression	According to studies, in the early stages of PD, 90-95% of patients exhibited pre-motor symptoms, with depression being the most common. It is considered one of the non-motor markers of disease development in the preclinical stage.
[42]	Narrative Review	Dysphagia	Dysphagia, a condition affecting 40-80% of people with PD, is a significant concern regarding functional swallowing, as it depends on adequate cognitive function, as well as somatic and autonomic sensory-motor functions.
[45]	Review	Urinary Dysfunction	Lower urinary tract symptoms occur in approximately 27-85% of PD patients and include nocturia, increased urinary frequency, and urgency. Additionally, bladder detrusor muscle hyperactivity, responsible for contraction during urination, is observed in 58% of untreated PD patients.
[49]	Narrative Review	Sexual Dysfunction	Epidemiological data show that decreased libido, deficiency, or lack of desire in sexual activities in women with PD ranges from 46.9% to 84%, while difficulty achieving orgasm occurs in 75% of these patients.

3.1 Sensory Symptoms

3.1.1. Hyposmia

Since PD is known to be a multisystem disorder, one of its main non-motor manifestations, which affects around 90% of patients, is hyposmia. Defined as a reduction in the ability to sense and detect smells, it is a highly prevalent symptom in patients and can precede the onset of motor characteristics by several years. Furthermore, in at least 10% of patients with idiopathic olfactory dysfunction, it may be related to an increased risk of developing PD [13]. Although it is assumed that early olfactory degradation is a result of selective exposure to the development of the disease, a contrary hypothesis is that exposures that trigger olfactory loss can lead to PD. It is worth noting the ability to use progressive hyposmia as a biomarker of cognitive decline and cholinergic denervation in PD patients, whose decreased quality of life and increased mortality rates are observed [14, 15].

3.1.2 Pain

Pain is a common non-motor symptom of PD with a prevalence of between 40 - 85% and progressively increasing as the disease progresses. However, it is constantly underestimated and undertreated, despite the significant impact it has on patients' quality of life. Pain can therefore be classified into five classes in terms of its clinical characteristics, namely radicular or neuropathic pain, musculoskeletal pain, dystonia-related pain, akathetic discomfort and primary or central parkinsonian pain. Pain is seen to be one of the first symptoms to appear in PD and although it is most often secondary to motor disability, up to 43% of patients present with “primary pain” in the early stages, when the classic motor symptoms of parkinsonism are not yet prominent. In addition, it is known that later on there is an accentuation of pain on the side of the body most severely affected by motor impairment, in which around 50% of cases of PD patients who have associated pain do not receive any analgesic treatment [16-18].

3.1.3 Visual impairment

Ocular and visual impairments in patients with Parkinson's disease are manifested in up to 70% of cases, including decreased sensitivity and color discrimination. As a result, and easily confused with a senile eye disease, visual complaints are described that include defects in eye movement, pupillary function and more complex visual impairment. Within this profile, patients suffer from alterations in visual acuity, contrast recognition, spatial perception disorders, pupil reactivity, eye movements, visual field sensitivity and visual processing speed. Thus, impaired visual and visuospatial functions end up affecting activities that are essential to the patient's daily life and are increased as the disease progresses, resulting in reduced efficiency and quality of life [19, 20].

3.1.4 Taste dysfunction

The involvement of taste in Parkinson's disease has also been elucidated, although with less emphasis and perception due to the reduced impact on patients' daily lives [21]. With this, due to the greater risk of the patient presenting unintentional weight loss, the relationship between smell and taste raises hypotheses of the expedited BMI below the expected, seen by the greater number of malnourished patients in PD [22].

3.2 Sleep Symptoms

3.2.1 Insomnia

Insomnia is a diagnosis of the patient's subjective symptoms, in which they report difficulty initiating sleep, maintaining sleep or waking up earlier than desired even with time and opportunity to sleep, associated with worries and disturbances [23]. PD patients most commonly suffer from insomnia, with 60% claiming sleep problems and 76%

claiming poor quality sleep. In addition, as PD and the degeneration of the nervous system progress, insomnia also increases in incidence and severity [24]. It is also worth noting that the disturbance of the sleep-wake cycle can further lead to the progression of the disease, resulting in nocturnal hypertension, nocturnal blood pressure equivalent to or greater than daytime blood pressure, metabolic abnormalities, thermoregulation and irregular hormonal rhythms [25].

3.2.2 Restless legs syndrome

Restless legs syndrome (RLS) is defined as a disturbance in the lower limbs, especially at night and at rest, in which the patient seeks movement for partial or total relief of this symptom. In Parkinson's disease, even with a difficult diagnosis due to multiple similar factors such as motor fluctuations, akathisia and neuropathy, the prevalence of RLS was 15.74%, with an association between dopaminergic dysfunction in PD and RLS [26]. It is also seen that a significant number of PD patients with PIS claim a delay in sleep onset and more severe sleep problems than patients without PIS, suggesting a significant link between the two diseases [27].

3.2.3 REM sleep behavior disorder

Classified as a sleep-related disorder, REM rapid eye movement sleep behavior disorder (RBD) is a very common symptom in PD and is a parasomnia-type disorder. With this, it is observed that the patient has undesirable episodic behaviors that occur at the beginning of sleep, during sleep or upon awakening. As a result, the patient exhibits abnormal behaviors such as movements, gestures and vocalizations, nightmares and loss of normal skeletal atonia, such as muscle contractions, kicks and fights. In view of this, this disorder is associated with one of the most significant clinical indicators of the future development of PD, characteristic of a prodromal phase, a longer duration of the disease and more advanced stages of PD [28, 29].

3.3 Neuropsychiatric symptoms

3.3.1 Cognitive dysfunction

As one of the most prevalent non-motor symptoms in PD, cognitive dysfunction presents at a rate of 20 - 33% with mild cognitive impairment (MCI), more than 40% of patients develop MCI within 6 years of diagnosis and 60 - 80% go on to develop dementia in PD. In this context, cognitive dysfunction is a common and debilitating feature, where a heterogeneous pattern is observed, with loss of memory, attention and executive skills being the main manifestations. It is also known that atrophy of the hippocampus can serve as a biomarker of initial cognitive decline in PD, including encoding and impaired memory storage [30-32].

3.3.2 Psicose

Psychosis in patients with PD is one of the most common manifestations and is characterized by being complex and disabling. It has an estimated prevalence rate of 43 to 63% in the more advanced stages of the disease and increases as life progresses. It is worth noting that the pattern of symptoms of psychosis in PD is different from that of other psychotic illnesses such as schizophrenia and other mood disorders [33]. With this, the aspect of psychosis in PD, called positive PD symptoms, consists of hallucinations of passage, delusions or hallucinations of presence [34]. Although psychotic symptoms used to be attributed to the side effects of dopaminergic drugs, in recent years it has been found that they are due to more complex intrinsic and extrinsic factors of the disease [35].

3.3.3 Language dysfunction

Language dysfunctions in patients with Parkinson's disease involve word impairment, increased frequency of grammatical errors, difficulties interpreting figurative language and semantic ambiguities. A significant deficit in verb processing has also been reported [36]. It is known that expressive language deficits can be elucidated at each stage of spoken language production, including linguistic formulation, severely reduced spontaneous speech, which makes verbal communication slower and less precise. Given this, the etiology of language deficits in PD is not yet fully defined, but most studies have highlighted an association with the patient's cognition. Other controversial studies have linked this finding to working memory and executive function [37, 38].

3.3.4 Anxiety

Because it seriously affects the quality of life of patients with Parkinson's disease and is one of the most prevalent problems encountered, anxiety is now considered an important part of the complete treatment of PD. About its predisposing factors, female gender, young age and the presence of motor fluctuations, among others, can be highlighted. As a result, various forms of anxiety are manifested, such as generalized anxiety disorder, social phobias and obsessive-compulsive disorders. In addition, there is also an essential increase in what is known as parkinsonian personality, accompanied by an increase in the severity of movement disorders and the development of the disease. In addition, the impact on the patient's quality of life can be highlighted, where the interaction between motor symptoms and anxiety results in a vicious cycle, where one often ends up triggering the other. There is a prevalence rate of 20 - 46% of patients with certain manifestations [9, 39, 40].

3.3.5 Depression

According to studies, in the early stages of Parkinson's disease, 90 to 95% of patients have pre-motor disorders, the most common of which is depression, which can be considered one of the non-motor markers of the development of the disease in the pre-clinical period of PD. As a result, most of the manifestations are given by depressed mood, anhedonia, low self-esteem, guilt towards relatives, irritability, bad mood and pessimism, in which suicidal thoughts can occur. It is known that the symptoms of depression usually change over the course of the illness, with affective disturbances manifesting themselves in the first three years of the illness and later, due to adaptation, a decrease in psycho-emotional interaction is observed. In addition, depression and PD share common symptoms such as reduced facial expression, trouble sleeping, fatigue, psychomotor retardation and reduced appetite, which contributes to the underdiagnosis of depression in PD patients [39, 41]

3.4 Autonomic symptoms

3.4.1 Dysphagia

Dysphagia, a disability that affects 40-80% of people with PD, has a significant warning point with regard to functional swallowing due to the fact that it depends on adequate cognitive function, somatic functions and sensory-motor autonomic functions. Although dysphagia usually worsens over time, the first signs can occur in the prodromal stages, when the disease is often not yet detected. As a result, patients with this dysfunction are subject to malnutrition, dehydration and increased mortality due to aspiration, which can lead to aspiration pneumonia. Pneumonia is known to be one of the main causes of hospitalization and death in PD [42-44].

3.4.2 Urinary dysfunction

Occurring in around 27 to 85% of patients with PD, lower urinary tract manifestations are reported as nocturia, increased urinary frequency, with an urgency to urinate. Also, hyperactivity of the detrusor muscle of the bladder, responsible for contraction

during urination, is seen in 58% of untreated PD patients [45]. Urinary tract infection (UTI) is one of the main causes of acute hospitalization in PD patients, with a risk of predisposition to urinary retention, where due to motor symptoms there is difficulty accessing the toilet [46]. In addition, it is known that patients with urinary symptoms have a greater predisposition to having motor and non-motor disorders, manifesting a rapid functional decline in the early years of the disease [47].

3.4.3 Sexual dysfunction

One of the most neglected disorders, which is detrimental to the lives of patients with Parkinson's disease, is sexual dysfunction with reduced sexual desire. Epidemiological data show that decreased libido, deficiency or lack of desire in sexual activities in women with PD range from 46.9 to 84%, while difficulty in reaching orgasm occurs in 75% of these patients. In men with PD, rates ranged from 27 to 83%, while decreased erection of the penis and the inability to achieve or maintain a penile erection ranged from 42.6% to 79%, the most common complaint in men. In addition to these factors, it is important to highlight underreporting in everyday clinical practice, with frequent omission by patients [48, 50].

3.4.4 Gastrointestinal tract disorder

The gastrointestinal tract (GIT) is divided into upper and lower. The main dysfunctions of the GIT can include symptoms such as dysphagia, gastroparesis and chronic constipation. It is known that the upper GIT comprises structures from the mouth to the stomach. In patients with PD, delayed gastric emptying is seen in 70 - 100% of patients, causing nausea, vomiting, early satiety and bloating. In the lower GIT, which includes structures from the small intestine to the anal canal, 50 - 80% of patients manifest symptoms of constipation because the mucosal barrier of the intestine is compromised, and these symptoms can present up to many years before the motor symptoms of PD [45, 51, 52].

4. Future prospects

As the second most common neurodegenerative disease, PD requires early diagnosis. It is known that when motor symptoms such as resting tremors, bradykinesia, rigidity and postural instability are present, the condition has already progressed. In this way, non-motor symptoms, which often occur years before the disease, play a fundamental role in early investigations. Thus, the identification of biomarkers in early diagnosis, together with the association of non-motor symptoms, will enable the early use of disease-modifying therapies in the prodromal phase [53]. It is known that there is currently no cure for PD, but the active investigation of molecular biomarkers is being strongly discussed as a means of clinical instruments with great value for early diagnosis, contributing to a significant improvement in motor symptoms, particularly in the early stages of the disease [54].

5. Conclusion

Through the data expressed in this article, we can see how important it is to recognize the progression of Parkinson's disease in each of its pre-clinical phases, demonstrated by the appearance of non-motor symptoms, since many of these precede the motor clinical symptoms by years. It is therefore essential to pay attention not only to classic symptoms but also to the study, recognition and investigation of prodromes to focus on obtaining early diagnoses.

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