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Premotor, nonmotor and motor symptoms of Parkinson's Disease: A new clinical state of the art

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ABSTRACT

Parkinson's Disease (PD) is a neurodegenerative disorder that affects dopaminergic neurons in the mesencephalic substantia nigra, causing a progressive clinical course characterized by pre-motor, non-motor and motor symptoms, which negatively impact the quality of life of patients and cause high health care costs. Therefore, the present study aims to discuss the clinical manifestations of PD and to make a correlation with the gut–brain (GB) axis, approaching epidemiology and therapeutic perspectives, to better understand its clinical progression and identify symptoms early. A literature review was performed regarding the association between clinical progression, the gut–brain axis, epidemiology, and therapeutic perspectives, in addition to detailing pre-motor, non-motor symptoms (neuropsychiatric, cognitive, autonomic, sleep disorders, sensory abnormalities) and cardinal motor symptoms. Therefore, this article addresses a topic of extreme relevance, since the previously mentioned clinical manifestations (pre-motor and non-motor) can often act as prodromal markers for the early diagnosis of PD and may precede it by up to 20 years.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by motor symptoms, systematized in a classic tetrad, defined by the acronym TRAP (tremor, rigidity, bradykinesia and postural instability) (Kalia & Lang, 2015;

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Zesiewicz 2019), and symptoms not motors (Li et al., 2021) that impair the quality of life of patients and cause high healthcare costs. Epidemiological studies show that this condition has a global prevalence of 200/100,000 individuals, with approximately one diagnosis per hour (Titova & Chaudhuri, 2018). Furthermore, the incidence increases from 5 to 10 times from the sixth to the ninth decade of life and leads to an increase ranging from 5/100,000 to more than 35/100,000 new cases per year (Simon et al., 2020). Additionally, the number of people with PD has been increasing worldwide and the number of diagnoses is expected to double by 2040 (Titova & Chaudhuri, 2018).

Regarding the pathophysiology, there is a presynaptic degenerative process that affects dopaminergic neurons in the substantia nigra, specifically in the pars compacta region of the midbrain, with the formation of Lewy bodies, which have toxic aggregates of α-synuclein (Munhoz et al., 2015; Campos-Acuña, 2019), a small protein highly expressed in presynaptic brain terminals that acts by modulating neuronal membrane stability, influencing presynaptic signaling and vesicular transport across the membrane (Atik et al., 2016). Thus, the clinical manifestations of PD arise. When compared to motor symptoms, these may be preceded between 10 and 20 years by non-motor disorders (Munhoz et al., 2015; Rossi et al., 2015).

Regarding the gut-brain axis (GBA), the main hypotheses about the pathophysiology of PD, especially that of Braak, in 2003, state that the intestine is the starting point for the development of the disease, since environmental pathogens, when invading the intestinal epithelium, would cause incorrect multiplication and aggregation of α-synuclein in neurons of the gastric myenteric and submucosal plexuses (Campos-Acuña, 2019, Mukherjee et al., 2016, Menozzi et al., 2021), which subsequently leads to the arrival of this protein, through the vagus nerve, in the substantia nigra and other areas of the central nervous system. It is also known that most of the parasympathetic innervation of the gastrointestinal tract (GIT) comes from the dorsal motor nucleus of the vagus nerve, one of the regions most affected in the initial stage of the disease (Jones et al., 2020; Felice et al., 2015; Pellegrini et al., 2015).

In addition to the GBA, it is also important to reiterate the clinical progression of PD, for a better understanding of its phases and periodic manifestations. On this subject, it is important to emphasize that this disorder is characterized by a neurodegeneration that can manifest itself in a very heterogeneous way (Silvia Cerri & Blandini, 2020; S. Cerri & Blandini, 2020) and other motor and non-motor symptoms appear as the disease progresses, following a clinical course that begins with its diagnosis. However, this condition may be preceded by pre-motor (or prodromal) symptoms in 20 or more years (Kalia & Lang, 2015), which are characterized as impaired sense of smell (anosmia, hyposmia), constipation, depression and REM sleep behavior disorder (Zesiewicz, 2019). Regarding additional non-motor conditions, these develop after diagnosis and with the evolution of the disease (Kalia & Lang, 2015). Along the progression, axial motor symptoms tend to appear, such as postural instability with frequent falls or even freezing of gait (Kalia & Lang, 2015; Zesiewicz, 2019).

Still in this context, non-motor manifestations are a set of conditions that may appear before motor alterations, which significantly compromise patients' quality of life (LeWitt, Chaudhuri, 2020) and include psychiatric symptoms, urinary and sexual dysfunctions, gastrointestinal problems, sensory deficiencies, circadian cycle disorders, hyposmia, unintentional weight loss, osteosarcopenia, among other disorders (Poewe, 2008; De Rui et al., 2020). Furthermore, in addition to being considered pathological alterations inherent to the pathophysiology of PD, these conditions can also present as adverse effects of drug therapy (Poewe, 2008).

It is extremely important to recognize the initial manifestations (Fig. 1), that is, the non-motor symptoms of PD, since they are prodromal markers that usually occur 10–20 years before the traditionally recognized motor disorders, bringing the possibility of instituting earlier treatments, which would improve the prognosis of patients. In this context, it is estimated that up to 80% of the dopaminergic cells in the nigrostriatal system are lost before the characteristic motor symptoms of PD begin to appear (), which highlights the alert for early diagnosis and treatment, reducing the progression of this neurodegenerative disorder.

In light of these circumstances, this research aims to compile non-motor conditions in Parkinson's Disease, relating them to the brain-gut axis, in order to address topics such as epidemiology and therapeutic perspectives, as well as to demonstrate the relevance of these conditions, both for understanding the pathogenesis of Parkinson's disease, and for stimulating the early identification of these non-motor

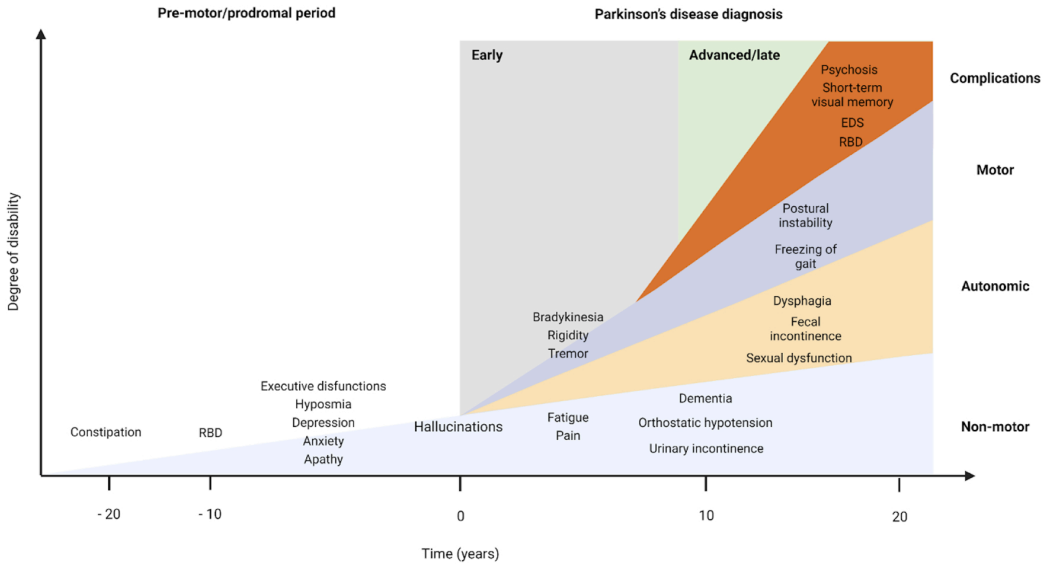

Fig. 1. Parkinson's disease (PD) symptoms onset and progression. PD non-motor symptoms (pre-motor/ prodromal) normally initiate 20 years before PD diagnosis, which is when normally motor symptoms are presented. As the disease progresses, other non-motor, autonomic and motor symptoms develop, as well as the potential onset of complications. EDS = excessive daytime sleepiness. RBD = REM sleep behaviour disorder.
Figure adapted from Kalia, Lang (2015).

disorders, improving the prognosis of PD by stimulating the search for new therapies with different targets and earlier.{{{Table 1}}}.

2. Results and discussion

2.1. Premotor symptoms

2.1.1. Constipation

Constipation is one of the manifestations of PD that may occur prior to the diagnosis of the disease and whose prevalence, severity and impact on well-being increase with the evolution of the disease (Salat-Foix, Suchowersky, 2012). That disorder may precede motor symptoms by up to 20 years and may affect approximately 20–29% of the population with PD (Rossi et al., 2015; Jones et al., 2020). Other studies show that its occurrence before motor symptoms in PD reached 87%, from symptoms such as constipation, which occurred before they developed bradykinesia, tremor, and rigidity (Perez-Pardo et al., 2017). Symptoms worsen during the course of the disease and malabsorption is often the reason why dopaminergic replacement therapy does not work. Malabsorption may be caused by delayed gastric emptying and/or prolonged transport times. Some patients even have the pills in their throats. Using quality of life scales, these disorders have been shown to be quite unpleasant for patients with PD. Dysphagia and weight loss due to malabsorption can result in life-threatening situations.

2.1.2. Anosmia

It is known that anosmia and hyposmia are considered the most reliable diagnostic predictors of pre-motor symptoms of PD (Paola Tirassa et al., 2021). Less than 90% of patients with PD have hyposmia (Haehner et al., 2009). There is good evidence that most patients with PD develop impaired sense of smell 4–6 years before they begin to experience motor impairment (Müller et al., 2003). Some studies claim that such symptoms appear early in PD, functioning as potent biomarkers in this disease, and it is argued that they progress after the onset of motor symptoms (De Rui et al., 2020). However, in opposition to the previously mentioned assumption, other recent studies claim that patients with progressive neurodegeneration do not demonstrate worsening of olfactory function, suggesting that olfactory function is not a useful marker to monitor disease progression, despite identifying patients at higher risk of conversion (Dall'Antonia et al., 2018). In addition, even though there are ways to test the olfactory function, such as the University of Pennsylvania Smell Identification Test (UPSIT or SIT) and the Sniff test, the results of this experiment can be falsified by the individual olfactory interpretation of each patient, demonstrating that this disorder is still too limited to be a reliable biomarker (De Rui., 2020).

2.1.3. REM sleep behavior disorder (RBD)

Regarding REM sleep behavior disorder (RBD), it is a parasomnia characterized by involuntary vocal and motor behaviors during REM sleep, in the context of vivid dreams with generally negative emotional content (Videnovic, 2018), which is characterized by usually aggressive and violent behavior and by demonstrating REM sleep without atony on polysomnography (Iranzo et al., 2006). Thus, it is demonstrated that individuals with isolated RBD have an increased risk of developing neurodegenerative diseases, such as PD, estimated at 18–35% in 5 years, as well as 40–75% in 10 years (Kalia, Lang, 2015). In addition, this disorder has reported prevalence rates in the population with PD between 4% and 70% and polysomnography-confirmed prevalence rates between 39% and 46% (Videnovic, 2018). Studies have investigated the possibility that other pre-motor signs, such as hyposmia, may potentiate the predictive value of RBD in the conversion to PD (Stiasny-Kolster et al., 2005).

2.1.4. Depression

Depression is characterized by a feeling of guilt, lack of self-esteem,

Table 1
Description of the premotor, nonmotor and motor symptoms of Parkinson disease.

Premotor Symptoms	Nonmotor Symptoms: Neuropsychiatric	Nonmotor Symptoms: Cognitive	Nonmotor Symptoms: Autonomic	Nonmotor Symptoms: Sleep Disorders	Nonmotor Symptoms: Sensory Abnormalities	Cardinal Motor Symptoms
Constipation	Depression	Executive dysfunction	Orthostatic hypotension	Insomnia	Anosmia	Tremor
Anosmia	Anxiety (mood disorders)	Memory loss	Constipation	Somnolence	Pain	Rigidity
Rapid eye movement (REM) sleep behavior disorder	Apathy	Dementia	Fecal incontinence	Excessive daytime sleepiness	Ageusia	Bradykinesia (or akinesia)
Depression	Impulsive control disorder		Nausea	Restless legs syndrome	Numbness	Postural instability
	Psychosis		Vomiting	Sleep attacks	Paresthesia	Gait disorder
	Anhedonia		Drooling	Periodic limb movements of sleep		
	Hallucinations		Urinary incontinence and urgency	REM sleep behavior disorder		
	Abulia		Sexual dysfunction	Vivid dreaming		
	Attention deficit disorder		Altered cardiac reflexes			
	Panic attacks		Olfactory dysfunction			

Legend. Premotor, nonmotor and motor symptoms of Parkinson disease. Premotor symptoms: Salat-Foix and Suchowersky., (2012); Rossi et al. (2015); Jones et al. (2020); Perez-Pardo et al. (2017); Paola Tirassa et al. (2021); De Rui et al. (2020); Videnovic et al. (2018); Borgonovo et al. (2017); . Nonmotor symptoms: Medonça et al., 2020; Weintraub et al., 2022; Poewe. (2008); Nassif, Pereira (2018); Angelopoulou et al. (2022); Carrozzino (2019); Starkstein, Leentjens (2008); Fan et al. (2020); Elefante et al. (2021); Praetner et al. (2021). Cardinal motor symptoms: Zesiewicz (2019); Elodie Kip (2022); Kalia, Lang (2015); Titova, Chaudhuri.,2018; Munhoz et al. (2015); Campos-Acuña et al. (2019); Moustafa et al. (2016); Bologna et al. (2019); Armstrong and Okun (2020).

sadness and remorse (Chaudhuri et al., 2006) and can appear at any stage of the disease, but it commonly appears at the onset of the illness, being, many times, one of the first clinical manifestations (Weintraub et al., 2022). Regardless of age, approximately 30% of all PD patients suffer from depression (Jellinger et al., 1999). Contrary to what happens with motor disorders, whose cardinal symptoms appear when 70–80% of the nigrostriatal nerve terminals are degenerated, depression can occur many years before the diagnosis of PD (Borgonovo et al., 2017). It is not that depression causes Parkinson's disease, but that a common pathology leads not only to impairment and malfunction of the dopaminergic system, but also of the noradrenergic and serotonergic systems.

Depressive symptoms usually anticipate clinical diagnosis based on motor disorders by more than 10 years (Medonça et al., 2020). Analyzing literary aspects, it is shown in a cross-sectional study, for example, involving depressed patients with PD and depressed patients without PD, that while the cognitive level of patients was similar in both groups, patients with PD had a different depressive profile, with fewer endogenous symptoms (feelings of guilt and sadness), but more somatic symptoms (problems of concentrating) (Weintraub et al., 2022). In contrast, other research showed nonsignificant differences in the psychopathology of depression associated with PD (Borgonovo et al., 2017). Regarding its importance, this condition is one of the main indicators of poor quality of life and functional disability, occurring in 40–70% of cases (De Rui., 2020). Depression and anxiety can commonly coexist and develop 4–6 years after the onset of PD motor symptoms. Depression occurs in about 35% of PD patients (Felice et al., 2016). Both can also be associated with asymptomatic periods, a consequence of fluctuation secondary to levodopa therapy (Weintraub et al., 2022). Depression is also a non-motor symptom (neuropsychiatric).

2.2. Non-motor symptoms (Neuropsychiatric)

2.2.1. Anxiety

Anxiety occurs in about 40% of patients with PD, with social phobia and generalized anxiety disorder (GAD) being its most common manifestations (Felice et al., 2016). With regard to its prevalence in the clinical phases of PD, it may be more stable than depression, which tends to prevail differently throughout the course of the disease (Weintraub et al., 2022). Furthermore, the few studies on pure anxiety and pure apathy during the early stages of PD have revealed an association between the extent of dopaminergic damage and the severity of these psychiatric symptoms, as seen for depression (Borgonovo et al., 2017). Regarding contributing factors, young age, female sex, presence of motor fluctuations and other factors are identified (Poewe, 2008).

2.2.2. Apathy

Apathy is one of the most frequent neuropsychiatric symptoms in PD (Audrey et al., 2016), which may occur alone or in association with depression and anxiety. Its relationship with the dopaminergic denervation process in the mesolimbic pathway is suggested, as well as a possible connection with serotonergic degeneration, widely known in the pathogenesis of depression and anxiety, especially in the ventral striatum, dorsal and subgenual regions of the anterior cingulate cortex, as well as as in the right caudate nucleus and right orbitofrontal cortex (Audrey et al., 2016).

Apathy is a condition often wrongly interpreted as fatigue in patients with PD, however, it is defined as a state of decreased motivation that manifests as a reduction in goal-directed behaviors; it can be characterized by reduced interests or emotions that cannot be attributed to a diminished level of consciousness, cognitive impairment, or emotional distress (Nassif and Pereira, 2018). In the context of PD, apathy can lead to poor response to the treatment of motor symptoms, increased public health expenditure, reduced quality of life for patients and their caregivers, in addition to an increased risk of developing dementia (Mele et al., 2020). Its prevalence varies according to the population, with a prevalence between 25% and 40% (Weintraub et al., 2022). Regarding dopaminergic therapy, it seems to improve apathy, although its mechanism in PD also involves a non-dopaminergic pathway (Weintraub et al., 2022). Regarding non-pharmacological interventions, the practice of physical exercises seems to improve apathy in PD, in addition to improving physical functioning, strength, balance and gait (Audrey et al., 2016).

Regarding the assessment of apathy in PD, a series of scales have been developed, such as the Lille Apathy Rating Scale (LARS), which is clinically valid for the diagnosis of apathy; the WHO-5 and the Neurasthenia Scale, which can be used as screening measures to assess the severity of apathy symptoms; and the Starkstein Apathy Scale (SAS), used to exclude the presence of apathy symptoms and to assess medication side effects (Carrozzino et al., 2019).

Apathy can be present in several neurodegenerative diseases, including Huntington's Disease (HD), Multiple Sclerosis (MS), Alzheimer's Disease (AD) and PD, affecting 17–70% of people with PD, a wide range of estimates. prevalence rate that reflects the vast heterogeneity with which apathy is defined in the literature (Mele et al., 2020).

Apomorphine, due to its increased activity on D1-type dopaminergic receptors, may have beneficial effects on frontal dysfunction generated by PD, which is very relevant in the context of apathy, as this, together with dysexecutive disorder, are characteristic symptoms of PD-related frontal dysfunction (Fernández-Pajarín et al., 2022).

2.2.3. Psychosis

Psychosis is associated with high rates of mortality and distress in the care team. That condition manifests as visual hallucinations and minor hallucinatory phenomena (illusory sensation of presence and passage) (Lenka et al., 2017). Delusions, illusions and hallucinations of other categories, such as auditory, tactile and olfactory, are more unusual than visual hallucinations and, when present, they usually coincide with visual hallucinations (Lenka et al., 2017). It is also known that psychosis is one of the most debilitating non-motor symptoms of PD (Lenka et al., 2016). Its frequency in PD increases with the course of the disease, reaching up to 60% prevalence and, in addition, its appearance is not influenced by dopaminergic treatment (Weintraub et al., 2022). In this context, risk factors include cognitive impairment, dementia, age over 65 years, advanced disease, longer duration, presence of sleep disorders, depression, visual disturbances, and use of the following medications: dopamine agonists, levodopa, amantadine, and anticholinergics (Munhoz et al., 2015). Treatment with dopamine agonists has been highlighted as an important risk factor for impulse control disorders (Macías-García et al., 2022).

The APOE gene has three alleles, ε2, ε3 and ε4, and it has been suggested in some studies that the APOE ε4 allele may increase the risk of psychosis in Parkinson's Disease (PDD) and play an important role in the earlier manifestation of psychotic symptoms in PD (Angelopoulou et al., 2022). Furthermore, in a recent study, the ANKK1 - GGrs2734849 - gene polymorphism was correlated with the development of PDP in patients treated with levodopa. Several studies have investigated the relationship between the polymorphisms of genes encoding cholecystokinin (CCK) and those encoding CCK receptors (CCKRs) with the development of PDP, but it has been suggested that the effect of these polymorphisms on PDP largely depends on, race and ethnicity; in addition, dopamine transporter (DAT) coding gene polymorphisms were also associated with a higher frequency of PDP in some studies, but more studies still need to be organized (Angelopoulou et al., 2022).

Furthermore, although PDP has some processes common to other psychotic disorders, such as schizophrenia, its neurobiology is different, with neuroimaging and neuropathology studies showing deficits in executive function and visual processing in the neocortex and in limbic structures, associated with imbalances in dopaminergic, serotonergic, and cholinesterase neurotransmission (Angelopoulou et al., 2022).

2.2.4. Anhedonia

Anhedonia refers to decreased interest or pleasure in response to

stimuli previously perceived as gratifying in a premorbid state, grouping together a set of phenomena reported as a complaint of inability to experience pleasure (Assogna et al., 2011). It can be considered a symptom of depression and schizophrenia, although it is not clear that the mental states involved are the same in both cases (Assogna et al., 2011). Regarding the treatment, it can be stated that L-dopa and pramipexole have a positive effect (Assogna et al., 2011).

2.2.5. Visual Hallucinations

Regarding visual hallucinations, it was reported in a recent study that the presence of minor hallucinations may occur in 42% of patients who did not receive treatment for PD and that in 33% of these patients, minor hallucinations appeared as premotor symptoms (Lenka et al., 2017). The appearance of minor hallucinations in the premotor stage or during the early stages of the disease has important clinical implications, as minor hallucinations foreshadow the later appearance of visual hallucinations (VA), which underscores the importance of prompt identification and treatment of mild hallucinations. as soon as possible (Lenka et al., 2017). In the context of hallucinations, visions occur in 15–30% of patients, while non-visual hallucinations (such as auditory, tactile and olfactory) in turn, reach 35% and delirium 4% (Weintraub et al., 2022, Lenka et al., 2016). Furthermore, regarding the hallucinogenic manifestations, these are usually benign, while the more serious ones such as delusions and paranoid ideation are associated with the progression of the disease (Chaudhuri et al., 2006).

Regarding the genetic basis of visual hallucinations in PD, it has been shown that the BIRC5 - BIRC5rs8073069 - gene polymorphism can reduce the risk of this phenomenon, which may be related to increased expression of survinin, which inhibits apoptosis, neuroinflammation and oxidative st4545tress; it was also shown that the polymorphism of the gene encoding Interleukin 6 (IL-6), IL-6rs1800795- is associated with a lower risk of visual hallucinations in patients with PD, since this polymorphism decreases IL-6 levels and this contributes for neuroinflammation (Angelopoulou et al., 2022). The APOEε4 allele, mentioned above, in turn, has been linked to an increased risk of visual hallucinations in PD patients without dementia and treated with levodopa, as well as the GPX1 gene polymorphism -GPX1rs1050450-, which can reduce glutathione peroxidase-1 activity, resulting in a weakening of the response against oxidative stress (Angelopoulou et al., 2022).

2.2.6. Abulia

Several studies brought different definitions of abulia, but there was a final consensus on eight characteristics that should be considered typical of this clinical manifestation, which are difficulty in initiating and maintaining intentional movements, poverty of spontaneous movements, reduction of spontaneous speech, increase in response time to consultations, passivity, reduced emotional responsiveness and spontaneity, reduced social interaction, and reduced interest in usual hobbies (Starkstein, Leentjens, 2008). Furthermore, this syndrome was still found after basal ganglia disorders (Starkstein, Leentjens, 2008).

2.2.7. Attention deficit

There are studies that link attention-deficit hyperactivity disorder (ADHD) and PD and confirm that there is an increased risk of PD among patients with ADHD, revealing that patients with PD had a significantly higher rate of prior ADHD diagnoses than patients without PD (Fan et al., 2020). In addition, 42.86% of PD patients with a previous diagnosis of ADHD had an age of PD onset of less than 50 years, which indicates that earlier ADHD may cause earlier ages of PD onset (Fan et al., 2020). It is also worth mentioning that dopamine deficits in the nigrostriatal pathway are a component of the triggering processes of both ADHD and PD and that the mechanisms which may explain the association between these two conditions include neurotoxic effects of stimulants, other environmental exposures and Lewy pathology (Baumeister, 2021).

2.2.8. Panic attacks

In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), anxiety spectrum disorders consist of 12 diagnostic entities whose panic attack is described as a “discreet period of intense fear or discomfort” in which manifestations such as palpitations, sweating, tremors, shortness of breath, chest pain or discomfort, nausea, dizziness, derealization or depersonalization, and fear of dying develop suddenly and can reach their peak within minutes (Praetner et al., 2021). With respect to anxiety and its subtypes, lifetime panic disorder patients had higher rates of psychiatric symptoms before PD, lifetime unipolar depression, treatment for current psychiatric symptoms, and more severe psychopathology (Elefante et al., 2021). Polymorphisms of genes encoding CCK and CCKR, in addition to being associated with the development of PDD, have also been correlated with the development of panic disorder (Angelopoulou et al., 2022).

2.3. Non-Motor Symptoms (Cognitive)

Cognitive deficit, according to most epidemiological studies, coexists with RBD and AV (Lenka et al., 2016), the latter being considered markers of a future cognitive decline (Weintraub et al., 2022). Cognitive deficit is also one of the conditions that is strongly associated with psychosis (Weintraub et al., 2022).

2.3.1. Executive dysfunction

Regarding executive dysfunction, especially fluency, it was demonstrated in a longitudinal study that it is altered in patients with prediagnosed idiopathic PD, opening the possibility for its classification as a prodrome symptom of PD (Silvia et al., 2020).

2.3.2. Memory loss

Memory impairment depends on many factors such as age at disease onset, disease duration, and severity of clinical symptoms (Ding et al., 2015). However, in PD, short-term memory is usually impaired while long-term memory remains intact (Ding et al., 2015). In addition, studies also state that in PD, short-term visual memory is affected and its defects can be attributed to the severity and motor performance of the disease, differently from short-term verbal memory, which generally doesn’t undergo changes (Ding et al., 2015).

2.3.3. Dementia

Dementia is one of the most debilitating symptoms of PD and may be present in more advanced cognitive deficits, being common in up to three quarters of patients with PD, according to longitudinal studies (Lenka et al., 2016). Furthermore, it has recently been suggested that Parkinson’s Disease with Dementia (PDD) is one of the greatest risk factors for mortality in PD, which underscores the importance of effective management of PDD (Takeda et al., 2014). It has also been reported that hyposmia, one of the most typical non-motor features of PD, is another predictive feature of PDD (Takeda et al., 2014). Risk factors that are predictive of PDD include older age and more severe motor dysfunction (Takeda et al., 2014).

2.4. Non-Motor Symptoms (Autonomic)

2.4.1. Dysphagia

Dysphagia is attributed to pharyngoesophageal motor abnormalities (Menozzi et al., 2021) and may be present in PD, especially in patients with advanced stages of the disease, being a common symptom in more than 80% of patients throughout the course of the disease (Menozzi et al., 2021; Choi et al., 2020). Through the use of Videofluoroscopic swallow study (VFSS) and Fiberoptic endoscopic evaluation of swallowing (FEES), in addition to the performance of a multidisciplinary team, it is possible to determine an adequate rehabilitation for the patient with PD who presents symptoms of dysphagia (Umemoto et al., 2020). Regarding its severity, it will depend on the stage of PD and, in

addition, another characteristic is that this dysfunction has little influence on the nutritional status of the patient (Menozzi et al., 2021). Although the prevalence of dysphagia in patients with PD is not as evident, the rate increases considerably 15 years after onset in the course of long-term clinical PD (Umemoto et al., 2020). The diagnosis of this disorder, in turn, is performed with the modified barium swallow test, which is non-invasive, consistent and accurate (Menozzi et al., 2021).

2.4.2. Urinary incontinence

Regarding urinary symptoms, those related to the lower urinary tract (nocturia, urgency and incontinence) are reported in approximately half of the patients with PD and, of these, approximately two thirds of them have urodynamic impact (such as a weak stream, urinary hesitancy, and a feeling of incomplete emptying) (Choi et al., 2020). In this context, a recent study found that this disorder affects patients with PD twice as often as elderly patients without PD, occurring in 27–39% of all patients with PD (Rana et al., 2015). Furthermore, the frequency of nocturia is reported in 60% of patients which is caused by overactivity of the urinary bladder detrusor muscle (98).

2.4.3. Sexual dysfunction

Regarding sexual dysfunctions, these play an important role in the deterioration of the quality of life of patients with PD and their partners, and can be present in half to two thirds of patients with PD, being greatly influenced by the presence of depression (Weintraub et al., 2022), in that men suffer from erectile dysfunction and ejaculatory problems and women from loss of lubrication and involuntary urination (Rana et al., 2015). Hypersexuality or aberrant sexual behaviors are more related to dopaminergic therapy, such as dopamine agonists (Choi et al., 2020, Rana et al., 2015). Furthermore, it is possible that dopaminergic drugs such as Levodopa and other antiparkinsonian drugs may affect sexual function in PD, although the contribution of Levedopa to improving sexual dysfunction is not yet clear (Sakakibara et al., 2011).

2.4.4. Olfactory dysfunction

Olfactory dysfunctions (Fig. 2), such as hyposmia and anosmia, occur in 70–90% of patients with PD, and it is important to emphasize their unresponsiveness to antiparkinsonian medications or other drugs (Choi et al., 2020, Morley et al., 2011). However, about 70% of affected individuals may not realize that their sense of smell is at its ability to function reduced. Furthermore, the olfactory test has been suggested as a useful tool for screening for PD, but it can be time consuming in the clinical period (Titova, Chaudhuri, 2018). In addition to its prevalence, olfactory dysfunctions are also predictors of the development of PD,

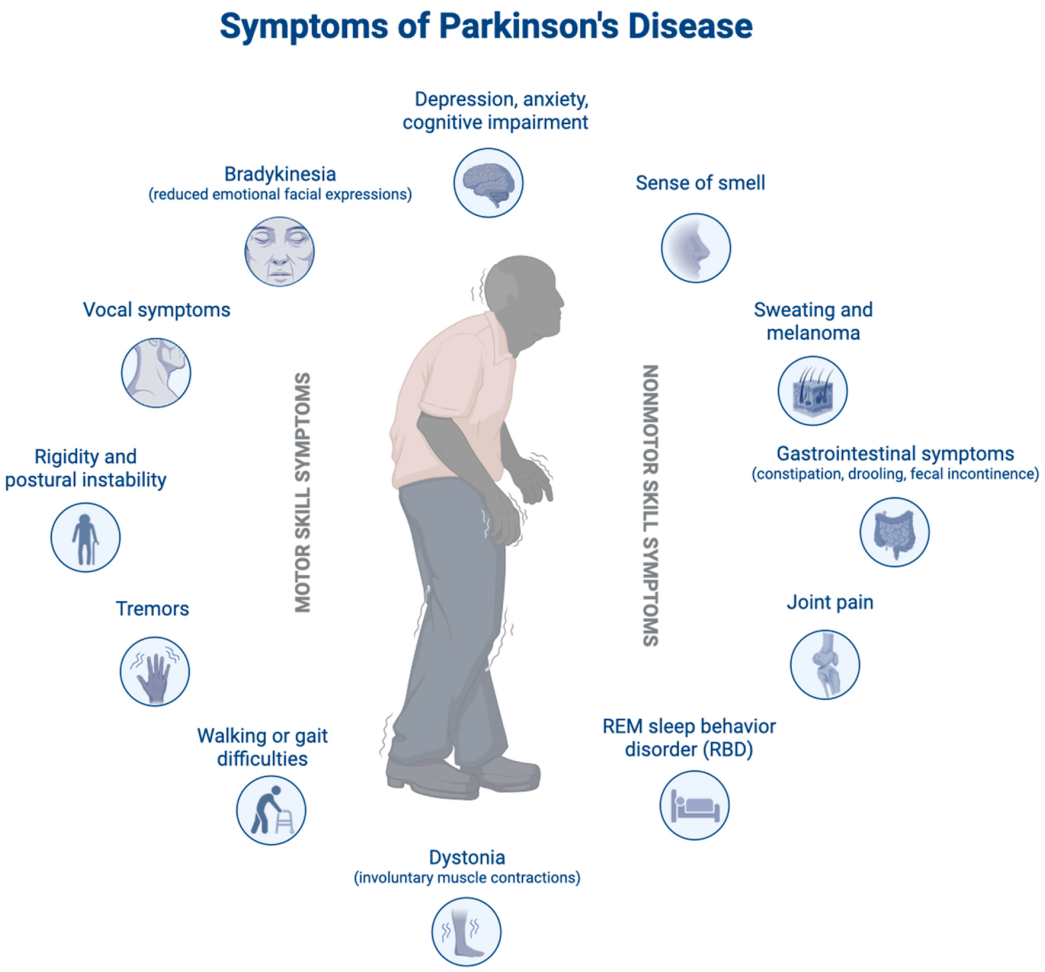

Fig. 2. Nonmotor and motor symptoms of Parkinson disease. Motor skill symptoms: Zesiewicz (2019); Elodie kip (2022); Kalia and Lang (2015); Titova Chaudhuri (2018); Munhoz et al. (2015); Campos-Acuña et al. (2019); Moustafa et al. (2016); Bologna et al. (2019); Armstrong and Okun (2020). Nonmotor skill symptoms: Salat-Foix and Suchowersky. (2012); Rossi et al. (2015); Jones et al. (2020); Perez-Pardo et al. (2017); Paola Tirassa et al. (2021); De Rui et al. (2020); Videnovic (2018); Borgonovo et al. (2017); Medonça et al. (2020); Weintraub et al. (2022); Poewe. (2008); Nassif and Pereira (2018); Angelopoulou et al. (2022); Carrozzino et al. (2019); Starkstein and Leentjens (2008); Fan et al. (2020); Elefante et al. (2021); Praetner et al. (2021).

being reiterated by cohort and longitudinal studies (Xiao et al., 2014). Several large-scale longitudinal studies are currently underway, such as the PARS (Parkinson Associated Risk Study) and TREND (Tübinger Assessment of Risk Factors for the Early Detection of Neurodegeneration) (Xiao et al., 2014). These dysfunctions are also described as factors that imply cognitive impacts (Morley et al., 2011), which tend to be greater in older people with PD who have hyposmia than in people who do not (De Rui et al., 2020).

2.4.5. Orthostatic hypotension

Orthostatic hypotension is defined as a fall in systolic blood pressure (SBP) of ‡20 mmHg and in diastolic blood pressure (DBP) of ‡10 mmHg (Tysnes et al., 2010) while standing or head-up tilted at least 60° within 3 min. When assuming the upright position, the patient may manifest dizziness, visual disturbances and impaired cognition that may precede loss of consciousness and affect 30–40% of patients. Furthermore, orthostatic hypotension is causally or associated with cognitive impairment in PD (Kang et al., 2022). Also in this context, one study provided evidence that orthostatic hypotension is more pronounced in PD patients with dementia than in PD patients without dementia. It is also worth mentioning that drugs used in the treatment of PD can induce changes in blood pressure (Tysnes et al., 2010). However, treatment with Droxidopa has shown improvement in symptoms (Marsili et al., 2022). Regarding the management of hypotension, in addition to the pharmacological approach, it is recommended to get up gradually, sleep with the head up, use elastic stockings, balance and break up meals (Choi et al., 2020).

2.4.6. Gastrointestinal dysfunction

Gastrointestinal symptoms are one of the most common non-motor manifestations of PD, being reported in 70–80% of patients (Fig. 2) (Perez-Pardo et al., 2017). In this context, attention is drawn to delayed gastric emptying, also called gastroparesis, which is responsible for symptoms such as early satiety, abdominal distension, nausea, vomiting and weight loss (Mukherjee et al., 2016; Pellegrini et al., 2015) and is present in 70–100% of patients with PD (Mukherjee et al., 2016). In addition, there is evidence that levodopa therapy can lead to worsening of gastric emptying, which may contribute to changes in absorption, with subsequent changes in drug response (Pellegrini et al., 2015). In contrast, another study observed that the delay in gastric emptying in patients with PD in the early stages of the disease, in the absence of any pharmacological treatment, did not differ substantially from that found in patients in more advanced stages, after treatment with levodopa (Pellegrini et al., 2015). As a possible treatment, a study in rodents provided evidence that acupuncture reduced the accumulation of alpha-synuclein in the colon and nervous system, improving inflammation (Qi et al., 2021).

2.4.7. Constipation

Constipation is the most frequently encountered gastrointestinal symptom (Fig. 2), being present in about 50–60% of patients with PD (Choi et al., 2020), or, according to other studies, in up to 80% of patients, with idiopathic constipation being one of the most common risk factors. important for the development of PD (Scheperjans et al., 2015). Regarding the pathophysiology, constipation is related to the accumulation of alpha-synuclein and neurodegenerative changes in the enteric nervous system (ENS) (Scheperjans et al., 2015). Constipation can manifest with hard stools, reduced bowel movements, bloating, abdominal pain, and straining during defecation (Menozzi et al., 2021). In addition, therapeutic bases include a diet rich in fiber and liquids, in addition to medications such as macrogol, lubiprostone and nizatidine (Mukherjee et al., 2016). It is also suggested that probiotic therapy may alleviate symptoms related to constipation and improve the general symptomatology of PD, including cognitive alterations and affective symptoms (Leta et al., 2021).

2.4.8. Fecal incontinence

Fecal incontinence, as well as other anorectal abnormalities (Fig. 2), can be assessed by manometric studies (Kim et al., 2011). According to literature data, these abnormalities are more common in patients with more severe conditions, however, more than 40% of patients without symptoms or with minimal symptoms also have manometric abnormalities (Kim et al., 2011).

2.4.9. Nausea and vomiting

It is known that nausea is one of the manifestations related to impaired gastric emptying (Fig. 2), a condition that also causes abdominal discomfort and early satiety (Sharma et al., 2019). In addition, the term “dyspepsia”, in turn, is used to group together various symptoms (nausea, vomiting, early satiety, abdominal distention, and heartburn) that arise from upper gastrointestinal (GI) dysfunction, usually abnormal gastric emptying (Salat-Foix, Suchowersky, 2012).

2.5. Non-motor symptoms (Sleep disorders)

Symptoms, in addition to RBD, are reported in 60–90% of patients with PD (Dos Santos et al., 2015). It is also described that there is a better prognosis for sleep disorders in individuals who practice physical exercises, especially in the case of moderate to high intensity activities, which subjectively affect sleep quality (Ivy et al., 2021). In addition, bright light therapy has been shown to be effective in improving sleep disorders and depression (Lin et al., 2021).

2.5.1. Insomnia

Insomnia is characterized as one of the sleep fragmentation disorders, which are prevalent in patients with PD, encompassing difficulties in starting sleep, maintaining sleep and/or waking up in the morning (Videnovic, 2018), present in 74–88% of patients (Antonini et al., 2013), or, in other references, up to 80% of patients (Videnovic, 2018), and triggering impairment of executive functions (Taximaimaiti et al., 2021). In this regard, patients with PD generally do not have significant difficulties falling asleep, however, they have difficulty maintaining sleep, causing sleep fragmentation (the most common sleep complaint in the population with PD), negatively impacting quality of life (Videnovic, 2018). In addition, insomnia is responsible for a decrease in total sleep time and is associated with the nocturnal reappearance of PD motor symptoms, interfering with sleep maintenance (Antonini et al., 2013). Thus, the etymology of insomnia in PD is linked to both the motor symptoms of the disease and associated comorbidities, medication side effects, dopaminergic degeneration that influence the basal ganglia, and the degeneration of cells that generate changes in the circadian rhythm (Mizrahi-Kliger et al., 2022). In PD, disturbances of the sleep-wake cycle can further worsen the progression of the disease and are characterized by nocturnal hypertension, nocturnal blood pressure equivalent to or greater than daytime, metabolic abnormalities, thermoregulation and irregular hormonal rhythms (Hunt et al., 2022). Regarding the risk factors for this condition, it is worth mentioning a more advanced disease and the female sex (Videnovic, 2018).

2.5.2. Somnolence

Excessive daytime sleepiness (EDS) is characterized by reduced alertness in the morning with persistent sleepiness, despite apparently adequate nighttime sleep (69), affecting $\geq$ 50% of patients with PD and which may be negatively associated with treatment with dopamine agonists (Chaudhuri et al., 2006; Antonini et al., 2013). This condition is related to high doses of levodopa ($\geq$ 1 g) and use of dopamine agonists, both of which are related to a higher score on the Epworth Sleepiness Scale (ESS) (Antonini et al., 2013), a scale that is measured in a short questionnaire, completed by the adult patient himself, to assess the degree of daytime sleepiness.

The score ranges from 0 to 24, and from 10 onwards, it is considered excessive daytime sleepiness. However, the use of L-dopa in

monotherapy was related to a lower score on the same scale (Del Pino et al., 2021). This disorder is associated with a decrease in quality of life and negatively affects the caregiver's burden in PD, in addition to causing worsening of the motor signs of parkinsonism with more prominent wear and tear (Videnovic, 2018).

Furthermore, risk factors include older men with more prominent cognitive, depressive, autonomic and other non-motor symptoms (Videnovic, 2018). Drowsiness in PD patients may have multifactorial interference, including the neurodegenerative process of the disease itself. A study proposes that EDS may be a risk factor or an early pre-motor manifestation of the PD synuclein-specific neurodegenerative process (Videnovic, 2018). In opposition, another report states that more recent evidence does not support that excessive sleepiness is a prodrome of PD (Videnovic, 2018).

2.5.3. Restless Legs Syndrome

Restless legs syndrome (RLS) is a sleep-related movement disorder whose diagnostic criteria encompass a need to move the legs along with an unpleasant sensation in the legs that worsens with inactivity and is relieved by movement (Videnovic, 2018). Therefore, during the night, symptoms worsen, causing poor sleep quality and the reason for medical consultation. Although it is a relatively easy clinical condition to be identified, it is still underdiagnosed and undertreated. The syndrome has a prevalence of between 8% and 50% in PD, compared to up to 10% in the general population (Huang et al., 2021), and is associated with good responsiveness to dopamine receptor agonists with 50% or more reduction from baseline in International Restless Legs Syndrome (IRLS) symptom scale scores. (Antonini et al., 2013). Patients with PD and RLS tend to have significant non-motor symptoms, such as depression, anxiety, autonomic dysfunction, and worse nutritional status (Videnovic, 2018). Finally, on the treatment, ropinirole and pramipexole and transdermal rotigotine can be used (Rana et al., 2015). However, dopamine blockers, anticholinergic agents, and antihistamines can exacerbate RLS and, therefore, need to be assessed and timely discontinued (Videnovic, 2018).

2.5.4. Sleep attacks

Sleep attacks are defined as sudden episodes of sleep with few warnings or no warnings of appearance, being extreme manifestations of PD (Antonini et al., 2013). These episodes deserve attention during medical evaluation, as they are associated with a higher risk of traffic accidents. In this condition, levodopa monotherapy is associated with a low risk of sleep attacks, while the combination of levodopa and dopamine agonists increases the risk by two or three times (Antonini et al., 2013). Non-ergot dopamine agonists are used as a monotherapy and as an adjunct therapy in the treatment of Parkinson's disease, they also have a higher incidence of psychiatric side effects, including hallucinations and impulse control disorders, as well as potential sleep attacks (sudden onset of sleep episodes) (Videnovic, 2018).

2.5.5. REM sleep behavior disorder

In the REM sleep phase, there is a neuronal activation and release of neurotransmitters that induce motor inhibition and muscle atony (Rana et al., 2015). However, when a disorder of this phase occurs, there is a loss of normal muscle atony, which can be exemplified by episodes of punching, kicking and screaming during sleep (19, Rana et al., 2015). In turn, REM sleep behavioral disorders (RBD) constitute a parasomnia characterized by vivid dreams associated with harmful or disturbing behavior, with a prevalence of 15–50% in PD patients and may precede motor signs (Antonini et al., 2013). These abnormal behaviors during REM sleep are known to be possible due to the loss of physiological muscle atony in the RBD, which represents a neurophysiological signature of the disorder (Videnovic, 2018) and may precede, by several years, the onset of the motor characteristics of PD (Diaconu et al., 2021). For the diagnosis of the disorder, the gold standard test is video-polysomnography, in order to confirm the abnormal motor behavior. However, in clinical practice, scales and questionnaires are used to screen for parasomnia (Diaconu et al., 2021). It is also known that certain drugs seem to work as a trigger for RBD, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants (Choi et al., 2020).

Furthermore, this "dream action" predisposes individuals with RBD and their bed partners to injury (Videnovic, 2018). With regard to symptoms, patients start to develop particular manifestations, such as worse gait scores and postural instability, lower amplitude of motor response to levodopa, higher frequency of orthostatic hypotension and visual color perception deficit (De Rui et al., 2020). Regarding therapy, Deep Brain Stimulation (DBS) therapy in the subthalamic nucleus (STN) and Internal Pallid Globe (GPI) stands out with a positive influence on sleep and wakefulness, particularly in REM sleep, on motor symptoms, but not on non-motors (Zuzuárregui et al., 2020). Small doses of clonazepam have also been found to reduce symptoms, along with donepezil, melatonin, and pramipexole (De Rui et al., 2020). In addition, providing a safe and less harmful environment during sleep for the patient and bed partner is also part of the treatment (Diaconu et al., 2021).

2.6. Non-motor symptoms (Sensory Abnormalities)

2.6.1. Anosmia/Hyposmia

Braak et al. defended the hypothesis that alpha-synuclein bodies are not only in the enteric nervous system, but also in the olfactory bulb, which ends up explaining the relationship between PD and olfactory dysfunction (De Rui et al., 2020). Olfactory disjunction can occur decades before the onset of motor symptoms and is therefore a prodromal non-motor symptom. In turn, reduced sense of smell (hyposmia) or lost sense of smell (anosmia) is seen in at least 80% of patients, being manifestations resulting from olfactory disorders resulting from this process (De Rui et al., 2020), although complete anosmia is demonstrated be unusual (Takeda et al., 2014). Regarding hyposmia, studies indicate that patients with this manifestation have a 3.84 times greater risk of having PD, and cognitive decline is usually greater in people who have it than in those who do not have it (De Rui et al., 2020). It is also worth noting that the degree of hyposmia tends to be milder in women than in men and is generally not improved by dopamine replacement therapies (Takeda et al., 2014).

2.6.2. Ageusia

Ageusia is another non-drug-responsive condition that, even so, has a frequency of appearance in PD of 9–54% (Choi et al., 2020), being less frequent than olfactory disorders, in addition to having a highly variable prevalence (De Rui et al., 2020; Cecchini et al., 2015). The most common causes of taste disorders are drug use (21.7%), zinc deficiency (14.5%), and oral and systemic diseases (7.4% and 6.4%, respectively) (Kumbargere et al., 2017). Impairment of taste can be caused not only by an altered threshold of taste and sensory pathways, but also by a variety of mental and physical disorders, including depression, lesions on the taste buds or mucous membranes, gum disease, dry mouth, gastrointestinal diseases, deficiency of zinc and medicines. Therefore, symptoms of altered taste may vary depending on the cause. Abnormal taste often induces loss of appetite, which results in malnutrition and impairs quality of life (Kumbargere et al., 2017). Various treatment modalities have been used to improve taste disorders. These include the use of zinc, transcranial magnetic stimulation, alpha lipoic acid, Ginkgo biloba, pilocarpine and acupuncture. The ability to manage taste disorders varies with each intervention (Kumbargere et al., 2017). Ageusia itself is rare, while dysgeusia is more common, but these and other taste disorders tend to become more frequent with advancing age (De Rui et al., 2020) and, in addition, are also evidenced as risk factors for dementia (Cecchini et al., 2015).

2.6.3. Pain

Pain is common in PD and can be of primary or secondary causes.

Such characteristics can be described as a constant pain, many times attributed to arthritis, or can be associated with dystonia that affects the feet and the toes, besides being able to mimic a radicular or neuropathic distribution (Bayulkem et al., 2011). This condition can be related to motor fluctuations, morning dystonia or secondary causes, such as musculoskeletal pain (Chaudhuri et al., 2006), as well as varies in prevalence between 30% and 83%, and can be influenced by numerous factors (Conte et al., 2013), but, when including all types of pain, this data reaches a value up until 85% (being the nociceptive type the most common) (Felice et al., 2016). Until recently, the pain associated with PD was not well evaluated, however, the current literature reports now agree that fluctuating pain is a common symptom frequently described by PD patients. This manifestation in PD patients can be directly related to the central nervous system dysfunction and not secondary to the disease's motor manifestations.

The current knowledge in the area supports the role of the basal ganglia's sensorial function through the modulation of information from other brain areas, such as the cortex, thalamus and substantia nigra, as a possible mechanism to explain why PD patients feel pain. It is known that in PD, the reduction of the dopaminergic input for the basal ganglia alters the sensorial perception and modifies the pain thresholds (Brefel-Courbon et al., 2005). It is also known that pain-related dystonia is reported in 40% of patients with PD and may fluctuate with levodopa therapy (Choi et al., 2020). Finally, some researchers have also reported that dopaminergic therapy leaves the pain threshold unchanged, while others have found that levodopa raises this threshold (Conte et al., 2013). Deep brain stimulation (DBS) is a well-documented treatment for severely disabled PD patients with motor fluctuations. Interestingly, previous studies have shown clinical pain relief after bilateral subthalamic nuclei DBS (STN DBS) (Kim et al., 2008). Finally, the use of cranial electrotherapy stimulation (CES) was explored by some authors, a non-invasive technique that applies a small amount of current through the head through ear clip electrodes, to treat pain in PD. A review of the use of CES in chronic pain concluded that CES was effective in reducing both headache and back pain, among others (Kirsch et al., 2000).

2.6.4. Paresthesia and numbness

It is also noteworthy that patients with PD often describe numbness and/or paresthesias/dysesthesias (Bayulkem et al., 2011). Such manifestations can be described as coldness, tingling, or tightness of muscles without objective evidence of sensory loss (Bayulkem et al., 2011). They tend to occur mainly during "off" periods (Bayulkem et al., 2011). Patients are also known to experience these symptoms more commonly in the legs than in the arms, however, the neck and face are rarely affected (Bayulkem et al., 2011). Furthermore, it can be stated that patients with RLS or akathisia very often describe these abnormal sensations (Bayulkem et al., 2011).

2.6.5. Hearing disorders

Hearing dysfunction as a manifestation of PD has received little attention from researchers, probably because hearing impairment is not a common complaint of PD patients (Vitale et al., 2012). There is evidence for altered detection of auditory deviations in a number of tasks, frequency discrimination tasks, for example, have suggested that PD patients have more difficulty in discriminating small threshold frequency differences compared to healthy controls (De Groote et al., 2020). Furthermore, most electrophysiological studies of auditory brainstem processing have indicated prolonged peak and interpeak latencies in PD patients compared to controls (De Groote et al., 2020). Finally, alterations in the auditory block response are also reported (De Groote et al., 2020).

2.7. Cardinal motor symptoms

Some of the cardinal motor symptoms have been described since the first studies on PD. James Parkinson began by describing, in 1817, a large number of people who presented tremor at rest, delayed gait, immobile posture, sleep problems and constipation and that, throughout the disease, there was an increase in a condition called paralysis agitans (Zesiewicz, 2019). Jean-Martin Charcot added bradykinesia and rigidity to the constellation of symptoms and named the disorder as Parkinson's Disease (PD) (Zesiewicz, 2019). It is described that the manipulation of the microbiota, in addition to having a positive impact on non-motor symptoms, may also contain classic motor symptoms (Valeria et al., 2016). Finally, it is described that, at the time of onset of motor symptoms, about 50% of nigro-dopaminergic neurons have already been degenerated (Elodie Kip, 2022).

2.7.1. Tremor

Tremor is often the first motor symptom to appear, affecting approximately 90% of patients throughout their lives (Zesiewicz, 2019) and 50% of patients may also present it with their arms outstretched (Zesiewicz, 2019), in addition to typically occur at rest. There are also symptomatic variations in Parkinson's tremor in its less atypical manifestations. In a systematic review, Mailankody, Netravathi and Kumar-Pal (2017) report 8 known types of this symptom, including: (Kalia, Lang, 2015) resting tremor, occurring between 4 and 6 Hz and whose main characteristic is disappearing when the patient presents voluntary movements and increase in stressful events; (Zesiewicz, 2019) action tremor, produced by intentional muscle contractions, (Li et al., 2021) posture tremor, with a frequency greater than 1.5 Hz, this subtype can be more disabling than most tremors; (Titova, Chaudhuri, 2018) kinetic tremor, occurs when the patient starts to move. This type of tremor was found mainly in terminally ill patients; (Simon et al., 2019) re-emergent tremor, which appears after a variable latency ranging from 0.79 s to 13 s between each episode; (Munhoz et al., 2015) Orthostatic tremor and pseudo-orthostatic tremor are exclusive tremors of the lower limbs and may vary widely in frequency (4–18 Hz); (Campos-Acuña et al., 2019) dystonic tremor, which occurs involuntary when the individual tries or insists on performing certain simple motor tasks; (Atik et al., 2016) internal tremor, which occurs in about 44% of patients, often more present in anxiety situations (64% in anxiety situations in contrast to 30% in patients at rest). Most of these subtypes can occur in a patient at different stages of the disease (Mailankody et al., 2017). Furthermore, it is known that tremors are almost always prominent in the distal part of an extremity, being more common unilaterally (Jankovic et al., 2008).

2.7.2. Stiffness

Stiffness is one of the main symptoms of Parkinson's disease (PD) (Tysnes et al., 2017). Decreased basal ganglia dopamine levels are strongly associated with akinesia and rigidity (Moustafa et al., 2016). Stiffness is characterized by increased resistance, usually accompanied by the cogwheel phenomenon, particularly when associated with an underlying tremor, present throughout the passive range of motion of a limb (Jankovic et al., 2008). It can occur proximally (neck, shoulders, hips) and distally (wrists, ankles) (Jankovic et al., 2008). The Froment maneuver, considered a reinforcement maneuver, can increase stiffness and is useful in detecting mild cases (Jankovic et al., 2008). In addition, such a manifestation may be associated with pain, and painful shoulder is one of the most frequent initial manifestations of PD, although it is commonly misdiagnosed as arthritis, bursitis, or rotator cuff injury (Jankovic et al., 2008). As for quantitative measurement, in recent decades, objective methods have been developed to quantify muscle tone. These methods are potentially useful for assessing stiffness in PD. One of these methods involves the use of servomotors, which mobilize a body segment at a desired speed. When this velocity is constant over the entire available range of motion (ROM), this is known as isokinetic dynamometry. This technique allows the collection of information regarding the resistance offered as an objective measure of stiffness (Mak et al., 2007). Furthermore, studies with a population with no evidence of dementia or parkinsonism report that the presence of rigidity, tremor, and

imbalance were associated with an increased risk of PD (Jankovic et al., 2008).

2.7.3. Bradykinesia

Bradykinesia is the most characteristic motor disorder of PD. This disorder justifies the term “paralysis” present in the expression “paralysis agitans”. It consists of a multifaceted clinical and pathophysiological manifestation. Historically, the term was defined only by the slowing of movements, but clinical and experimental studies suggest that the definition also encompasses the reduction of amplitude (hypokinesia), the absence of movement (akinesia), and the "sequence-effect", reduction of movement. additional amplitude and speed with repetitive and continuous movements. Dopaminergic therapy improves bradykinesia in general, but variably affects each of these aspects, in addition to having no significant impact on the “sequence-effect”. Thus, it is understood that the presentation of bradykinesia may vary among patients depending on the disease subtype, stage of progression, medications and other interventions (Bologna et al., 2019).

Dyskinesia, in turn, is also a disorder that involves motility, but, in this case, causing choreoathetoid movements induced by Levodopa, usually occurring years after the beginning of therapy, and at times when the drug reaches its peak concentration in the brain. Despite being severe in only 3% of Levodopa-treated individuals, dyskinesia promotes medication changes in 60% of patients, possibly due to social embarrassment and interference with daily tasks (Bologna et al., 2019; Armstrong et al., 2020; Nonnekes et al., 2019).

2.7.4. Postural instability

Postural instability usually appears about a decade after the initial diagnosis and is the condition most associated with falls in PD (Zesiewicz, 2019). The "pull-test" is used to assess this disorder: With the patient standing, a quick forward or backward thrust is performed on his/her shoulders. If more than 2 steps are needed to restore posture, a positive test is shown. Dopaminergic therapy, despite improving axial motor symptoms, has modest efficacy in treating instability (Jellinger et al., 1999). Deep brain stimulation (DBS) of the pontine peduncle nucleus, on the other hand, has shown good results in correcting postural instability and gait disturbances (Lin et al., 2020). Changes in microbiota composition, in particular the abundance of Enterobacteriaceae, are positively associated with the severity of postural instability and gait difficulty in patients with PD (Valeria et al., 2016).

2.7.5. Gait disorders

Gait disorders in Parkinson’s disease (PD) are among the most disabling of the disease, as they significantly limit mobility and often result in falls and fall-associated injuries. They range from a slowed, short-step gait to gait freezing, which is characterized by sudden and relatively brief episodes of inability to produce an effective forward step. Interestingly, the rostromedial striatum, a region involved in generating goal-directed movements, is usually less affected in patients, so that the automatic aspect of gait is impaired, but improves as long as the patient maintains conscious control of walking (Nonnekes et al., 2019). It is also mentioned that, after a continuous analysis of 17 years of disease, 80% of patients with PD reported freezing of gait and falls (Kalia, Lang, 2015).

2.8. Treatment

Finally, the treatment for PD is multifactorial, not having a specific one that stops or stops the progression of the disease. However, levodopa, which is the prodrug of dopamine, is the most common standard of therapy for these patients, in addition to dopaminergic drugs that function as a symptomatic treatment and aim to correct motor symptoms. Approaches such as DBS and treatment with levodopa-carbidopa enteral suspension may help individuals with medication-resistant tremor, Wearing-off (WO) phenomenon and dyskinesias. In addition, neurorehabilitation approaches can provide relief from treatment-resistant symptoms and signs through behavioral adaptations that bypass faulty motor circuits. The aforementioned measures include wearable technologies (such as those provided by smart glasses), gaming techniques, and telemedicine (Rana et al., 2017).

Regarding non-motor/pre-motor symptoms, many drugs used act on neurotransmitters other than dopamine (serotonin, norepinephrine, acetylcholine). Like motor conditions, treatment does not modify the progression of the disease. The approach is symptomatic, following patterns similar to those already used for the same symptoms in the general population, not affected by PD (Armstrong et al., 2020). It is also known that manipulation of the microbiota in the GIT, in order to make it healthy, has a positive impact on the quality of life of PD, reducing non-motor symptoms (such as pain, depression and constipation), and may even contain the classic motor symptoms (Rossi et al., 2015, Ekker et al., 2016; Alfonsetti et al., 2022).

3. Conclusion

Given the circumstances discussed, this article emphasizes the importance of understanding the clinical progression of Parkinson’s Disease, evidencing pre-motor, motor and non-motor symptoms of this neurodegenerative disorder, as well as the high prevalence of the aforementioned manifestations of the disease. Regarding pre-motor symptoms, it is concluded that these are extremely relevant for an early identification of PD, as such symptoms tend to appear several years before the stereotyped classic motor symptoms, which usually only appear after extensive neuronal degeneration. Emphasizing the importance of early diagnosis and treatment of this disease. In addition, the non-motor symptoms scored in this article are extremely significant and may even be confused with everyday manifestations in the life of a portion of the population (such as constipation, anxiety and depression).

Finally, the present study highlights, once again, the need for a better understanding of the clinical course and symptomatic management of the disease, seeking a better quality of life for sick people.

Conflict of interest

The authors declare that they have no conflicts of interest. All authors read and approved the final manuscript.

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