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ASSOCIATION BETWEEN NON-MOTOR SYMPTOMS AND FALLS IN INDIVIDUALS WITH PARKINSON'S DISEASE: INTEGRATIVE REVIEW

ASSOCIAÇÃO ENTRE SINTOMAS NÃO MOTORES E QUEDAS EM INDIVÍDUOS COM DOENÇA DE PARKINSON: REVISÃO INTEGRATIVA

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Abstract: Introduction: Parkinson's disease (PD) is a neurodegenerative disease that affects the basal ganglia, more specifically dopamine, closely related to the mechanisms of reward and reinforcement of behaviors. This explains the number of individuals with PD with non-motor symptoms, such as depression, anxiety, impulsivity, pain, insomnia, and mood changes. It seems that there is a strong participation of non-motor symptoms in the fall. However, few studies show an association or not with falls in these individuals. **Objective:** To review the literature on the association between non-motor signs and symptoms and falls in individuals with PD. **Methods:** This is a literature review. Research carried out in the Pubmed, Scielo, Lilacs and Medline databases between October and November 2021. Case-control or cohort studies were included that had the theme: non-motor signs and symptoms of individuals with PD associated with falls, according to the NMS SCALE Those who did not appear on the scale, as well as those duplicated in the databases, were excluded. **Results:** Search resulted in 33 and only 12 were selected, with a total of 1467

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patients studied. Depression, orthostatic hypotension and sleep, urinary and cardiac disorders were some of the non-motor symptoms associated with falls in individuals with PD. **Discussion:** Non-motor symptoms in PD have become increasingly limiting functionality and motricity in these individuals and strong influencers of falls, one of the major causes of death. **Conclusion:** due to the scarcity of studies, it is suggested the elaboration of studies that associate non-motor symptoms and falls in the population with PD.

Keywords: Parkinson Disease; Anxiety; Sleep initiation; Accidental falls; Review.

INTRODUCTION

Parkinson's Disease (PD) is a neurodegenerative disease that affects the black substance of the midbrain, more specifically dopamine, which is closely related to the mechanisms of reward and reinforcement of behaviors, that is, to motor symptoms. However, it is already recognized that the pathophysiology of PD describes the activation not only of the motor area of the brain, but also of areas such as the hypothalamus, brainstem and limbic system, directly related to the emotional. This explains the number of individuals with PD with non-motor symptoms, such as depression, anxiety, impulsivity, pain, insomnia and mood change[1-3].

The most common motor signals are gait disorders, such as bradykinesia, gait freezing, step and stride reduction and postural changes that modify its center of gravity forward, providing recurrent falls[4]. The fall in PD is an aggravating, debilitating and often recurrent problem, with a reported high incidence of at least one fall per individual and a great tendency to recurrent falls in a period of one to 4 four years [5-7].

With the advancement of studies on non-motor signs and symptoms in individuals with Parkinson's, it seems that there is a strong participation of these elements in the fall[8]. Previous research has identified some risk factors related to recurrent falls, such as freezing[9-10], reduced balance and mobility [5,7,11] and other non-motor symptoms, such as fear of falling and cognitive impairment [5,7,12]. However, the findings in the literature are still inconsistent with regard to the association between non-motor symptoms and falls in individuals with Parkinson's. Thus, the present study aims to review in the literature the association between non-motor signs and symptoms and falls in individuals with PD.

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METHODS

This is a literature review. The research was carried out in the Pubmed, Scielo, Lilacs and Medline databases, between the months of October and November 2021, by two independent authors. The search for keywords occurred from the analysis of the Scale for the Evaluation of Non-Motor Symptoms of Parkinson's Disease (NMS SCALE), in English, Spanish and Portuguese, in that order. They were: anxiety; impulsivity; depression; mood; cognition; sleep quality; fear of falling; fatigue; hallucinations; hypotension; attention/memory; sialorrhea/constipation/swallowing; urinary incontinence/fecal incontinence; sex; pain/sweating/taste/smell; Parkinson's; and falls.

The Boolean descriptors and and or were used when there was more than one word for the same term described in the NMS SCALE scale and represented by a slash "/". The crossing performed was one keyword at a time "and Parkinson and falls". Observational case control or cohort studies were selected in which the population was composed of individuals with PD and that addressed the association or not of non-motor symptoms with this sample. Those who did not present themselves according to the NMS SCALE scale were excluded, as well as the duplicates in the databases. In the first phase of the research, the titles and abstracts were read by two independent authors and those studies that met the eligibility criteria were selected for full reading.

RESULTS

33 articles were found in the databases in the first phase of the research. However, four of them were not available for full reading, even after establishing contact with the authors, and, therefore, were excluded. Thus, the final result consists of 28 studies found in Pubmed and one study found in the Medline database.

After reading the full 29 studies, of these, 17 were excluded by the outcome and only 12 were selected, following the inclusion and non-inclusion criteria (Figure 1). The characteristics of the selected studies are detailed in Table 1.

Figure 1 – Flowchart of the integrative review. Salvador, BA, BR, 2021.
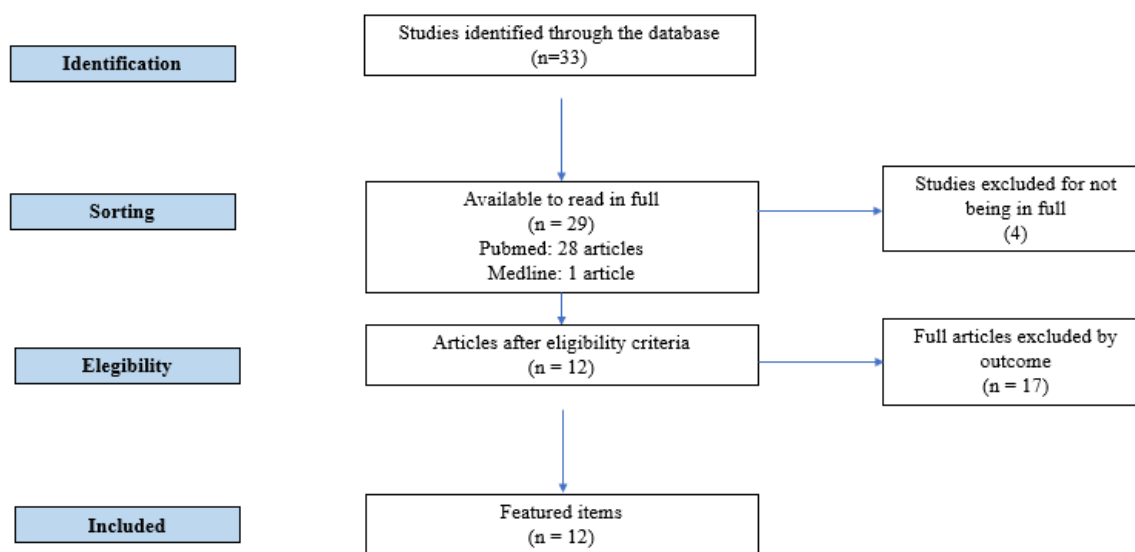
Source: Own elaboration.

Of these 12 selected studies, six are cohort and six are of the case-control study type, with a total of 1467 patients studied. Among the non-motor symptoms addressed in the studies are depression, fear of falling, fatigue, cognition, drowsiness, attention, impulsivity, orthostatic hypotension and sleep, urinary and cardiac disorders.

Table 1 – Characteristics of the included studies, Salvador, BA, Brasil, 2023.

Author/ year	Study Design/ time	Amostra/ gender	Age	Parkinson Gravity	Domain/ Assessment Instrument	Goal	Result
Allcock et al., 2009[13]	Prospective cohort / 1year	103 masc 61 fem T=164	71,2 anos	Scale (UPDRS III)−19,0	Depression/G DS15 Cognition/M MSe Atention/CDR	Whether the association between reduced or fluctuating attention and documented gait instability would be equivalent to	DS15 did not differ between the groups (p = 0.06). MMSE had no difference. CDR as a risk for dichotomous falls suggested an association of fall with reduced continuity of care (p

							an increased risk of falls in real life.	= 0.03), but not with other indices of attention.
Bryant *et al.*, 2012[14]	Case control/ 6 months	41 masc 13 fem T= 54	71,9 years	Hoehn and Yahr – Mild or moderate	Fatigue/IFS Drowsiness/ESE Depression/CES-D-10	Compare fatigue, sleep dysfunction and depressive symptomatology in individuals with PD who had fallen at least 1x (at a time) in the last 6 months for those who did not fall in this period.	Fallers reported more fatigue than non-fallers (p = 0.029), there was no difference in cognitive fatigue (p = 0.874). Drowsiness there was no difference (p = 0.43). Fallers had more depressive symptoms than non-fallers (p = 0.01).
Camicioli *et al.*, 2010[15]	Prospective cohort / 1year	42%fem T=102	71,5 Years	UPDRS	Cognitive/(CCDRSum> 0)	Identify risk factors for falls in a group of patients with PD and dementia compared to a community based on age and sex in the control group.	Patients with altered cognitive conditions were more prone to falls than the control group.
Kataoka *et al.*, 2011[16]	Case control /	14masc 16fem T=30	68,3 Years	Hoehn-Yahr internship III UPDRS II	Fear of falling/ Questionnaire	Investigate factors related to falls.	Fallers had a significantly greater fear of falling than non-fallers and was significantly related to the fall in the analysis with a single

							logistic model (p = 0.005).
Lindholm et al., 2015[17]	Cohort	T=141	68 Years	UPDRS III - 13	Fatigue/(FACIT-F) Fear of falling/FES	Determine the factors associated with future falls and/or near falls in people with mild PD.	Three factors were independent predictors of falls and/or near falls: fear of falling (OR = 1.032, p <0.001), history of close falls (OR = 3.475, p = 0.009) and retropulsion (OR = 2.813, p = 0.035).
Michałowska et al., 2005[18]	Case control/	29masc 31fem T=60	67,7 Years	Hoehn-Yahr 1-5 UPDRRS I, II, III, 45,43	Interview with neurologist Cognition/ minimal Orthostatic hypotension / Schellong QV/PDQ-39	Investigate the prevalence of the different causes of falls in PD and evaluate the influence of falls on quality of life (QoL).	Of the non-motor symptoms that caused falls were coexisting neurological disorders (6.5%), cardiac disorders (6.5%) and symptomatic orthostatic hypotension (3.2%).
Rudzinska et al., 2013[19]	Prospective Study/ 1 year	T=100	67,2 Years	UPDRS III - 48,9 Hoehn and Yahr	Depression/ hamilton Cognitive/ MMSE Neurological/ EEG, Cardiac NMR/ ECG	Prospectively analyze the direct causes and consequences of falls in patients with PD compared to the control group.	The analysis of the direct causes of falls revealed that the most common falls due to non-motor symptoms were neurological and sensory disorders (mainly vertigo) (12%) and orthostatic hypotension (4%).

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Sakushima et al., 2016[20]	Prospective Cohort / 6 months	40masc 57fem T=97	70,2 Years	Hoehn e Yahr	Urinary disorders / OABSS	Identify the association between falls and urinary disorders in PD.	The frequency of urination was not related to the fall; however, mild urinary urgency was more associated with the fall than severe (e.g. 0.05). Mild urinary urgency was also associated with the time until the first fall and the frequency of falls.
Smulders et al., 2014[21]	Prospective cohort / 6months	T=388 66% masc	65,8 years	Hoehn e Yahr-3 UPDRS	Impulsivity/ Barratt Impulsiveness Scale	Investigate whether impulsivity is related to the risk of falling in patients with PD.	Total impulsivity scores were higher in recurrent fallers (59.5) compared to non-fallers (56.8; p = 0.012). This effect was predominantly driven by higher scores on the attentional impulsivity subscale (p = 0.003).
Spindler et al., 2013[22]	Retrospective Study	120masc	71,4 Years	Hoehn e Yahr-2	Sleep disorders/ Epworth Sleepiness Scale (ESS)	Investigate the association of daytime sleepiness and falls in individuals with PD.	The fallers were significantly more likely to have excessive daytime sleepiness than the non-fallers (40.3% vs. 20.7%, p = 0.02.). Other factors associated with falls in the unadjusted analysis were depression (OR 3.9, 95% CI 1.6-9.4, p

<0.01) and cognitive impairment (OR 2.8, 95% CI 1.3-5.8, p <0.01).

Thomas et al., 2010[23]	Cohort	34fem T=102	70 years	Hoehn-Yahr	Fear of falling/FES	Examine the association between the frequency of falls and fear of falling among participants with idiopathic PD.	The FES also correlated with the number of falls (rho = 0.32, p = 0.001).
Wood et al., 2002[24]	Prospective Study/ 1year	52mas T=109	74,7 years	Hoehn-Yahr-2	Orthostatic hypotension/photoplethysmography Autonomic function/ standard tests32	Investigate predictive risk factors for fallers of patients with PD.	None o f the cardiovascular or autonomic data were associated with the fall. There were also significant associations between disease severity, balance impairment, depression and fall.

DISCUSSION

In the present study, it was observed that the non-motor symptoms most addressed in the studies are depression, fear of falling, fatigue, cognition, drowsiness, attention, impulsivity, orthostatic hypotension and sleep, urinary and cardiac disorders.

In more recent times, non-motor symptoms in PD have become increasingly limiting functionality and motricity in these individuals and strong influencers of falls, being one of the biggest causes of death. Through biological plausity, studies show how PD and motor and non-motor signals

relate, since the substantia nigra of the midbrain has an intrinsic activity in both neurophysiological activities, resulting from this process the disorder in dopamine[1,7,13].

Voon et al. [2] sought in their study to review the recent advances in the epidemiology and pathophysiology of impulse control disorders in PD. The research was multicentric, of cross-sectional characteristic, and showed that the behavioral changes were modified, such as: depressive symptoms, anxiety, obsessive search for novelty and impulsivity[2].

Corroborating, Weintraub et al. [3] tested the need to alert Parkinson's patients treated with dopamine agonist who should be advised of the risk of developing impulse control disorders. The monoaminergic systems that originate from nuclei in the brain stem and midbrain protrude through the cortex and limbic system. These systems modulate and integrate the cortical and subcortical areas related to psychomotor activities, appetite, sleep and mood. Therefore, there is not only involvement of a brain area, but a sequence of events. The brainstem, for example, is responsible for sleep and wakefulness, which leads to changes in the quality of sleep of these individuals[3].

However, there is a divergence in the literature regarding sleep, however, associated with the fall in individuals with PD. Bryant et al. [14] evaluated in their study the relationship of sleep disorders and fall in individuals with PD and no significant difference was found between fallers and non-fallers[14]. Spindler et al. [22]., disagree, because, in a retrospective study, they observed that fallers were significantly more likely to have excessive daytime sleepiness than non-fallers[22]..

The subcortical area is responsible for thought processing and decision-making. With this, depression may be related to neurotransmitters: dopaminergic mesocorticolimbic projections, serotonergic raphe nuclei of the brainstem and noradrenergic in the locus ceruleus. Dopamine has an influence on mood and the depressive symptomatology becomes more evident in the off period. The other possible non-motor signs are anxiety, social anxiety, impulsivity, disorders, appetite, sleep and gastrointestinal disorders. This has repercussions on the quality of life, since it is multifactorial, involving physical, emotional and social aspects of the individual[25].

Bryant et al. [14] also compared fatigue, sleep dysfunction and depressive symptomatology in individuals with PD, who had fallen at least once in the last 6 (six) months, in relation to those who did not fall in this period. With regard to depressive symptoms, fallers had more depressive symptoms than non-fallers[14]. In addition, Spindler et al. [22] agree with their result, unlike Allcock et al. [13], who did not observe a significant difference between depression of fallers in individuals with Parkinson's[13]. Wood et al. [24] demonstrated an association between depression and falls, but not between cardiovascular disorders and falls, whose symptom was also evaluated in the study [24]. On the other hand, Michalowska et al. [18] disagree, with regard to cardiac disorders and fall in individuals

with PD, since they observed that cardiac disorders were of the non-motor symptoms evaluated that caused fall in their control case[18].

Anxiety as another important non-motor symptom in PD is a normal part of life. People are always worried about some things, however, not all people have anxiety to the same degree. Nowadays, fear and the anxious state are not completely independent. It's probably impossible to feel afraid without being anxious. Being anxious involves anticipation, but the nature of anticipation in each one is different: the fear of anticipation happens when it involves a threat that can cause damage, while anxiety involves uncertain anticipation about the consequences of the threat that is not present and may not occur [26].

In this review, no study observed anxiety alone with falls in individuals with PD, but Kataoka et al. [16], Thomas et al. [17] and Lindholm et al. [23] addressed the association of the fear of falling with the fall in PD, since anxiety is directly involved in fear. However, both obtained a significant p value with regard to the risk of falling for these individuals.

FINAL CONSIDERATIONS

Given this scenario, it is concluded that depression, fear of falling, fatigue, cognition, drowsiness, attention, impulsivity, orthostatic hypotension and sleep, urinary and cardiac disorders are non-motor symptoms related to falls in individuals with PD. However, due to the scarcity of studies, it is suggested to develop more studies that associate non-motor symptoms and falls in the population with PD.

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