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Dor na doença de Parkinson

Pain in Parkinson's disease

Nuno Miguel dos Santos Vila-Chã

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Summary

Background

Classically, Parkinson's disease (PD) has been described as a motor disorder with bradykinesia, tremor at rest, rigidity, and postural instability as cardinal symptoms. Currently, PD is recognized as a complex disease that also includes non-motor symptoms such as autonomic dysfunction and neuropsychiatric, sleep, and sensory disorders. It has been recognized that PD is a highly heterogeneous disease and patients with PD present and progress in diverse ways and it has been proposed that there are different subtypes of PD.

Pain is a heterogeneous and disabling non-motor symptom of PD with a prevalence of up to 85%. The diagnosis and distinction of different pain subtypes in PD is essential for the evaluation of PD pain. There are different pain subtypes in PD, distinct from each other as defined by Ford's classification, are distinct from each other. Central parkinsonian pain seems to result exclusively from PD. Currently, the risk factors for pain in PD are not fully established. The pathophysiology of pain in PD is still unclear, but clinical, neurophysiological, and functional imaging studies have demonstrated alterations in the processing and interpretation of pain stimuli in PD patients. The neurodegenerative process that occurs in PD affects pain-related structures and pathways at multiple levels of the nervous system, including changes in non-dopaminergic pathways and structures. Most PD patients with pain are not treated for pain, and pain management in PD is not yet fully established.

The characteristics of central parkinsonian pain in PD, its relationship with motor and other non-motor symptoms, and the features of the Park pain subtype remain largely unknown.

Aims

The main objectives of the research that constitutes this PhD thesis were as follows: to determine the prevalence and characteristics of pain and pain subtypes in PD; to investigate the relationship between central parkinsonian pain and demographic and clinical characteristics of patients with PD; to explore the relationship between

pain and central parkinsonian pain, and other non-motor symptoms; and to perform a clinical characterization of the putative Park pain subtype of PD.

Participants and methods

To achieve the objectives of this research project, we conducted a large observational study in 292 PD patients followed at the Movement Disorders Outpatient Clinic of Centro Hospitalar Universitário do Porto. The patients were evaluated in *off* and *on* medication conditions and multiple demographic and clinical data were collected based on a semi-structured interview, validated instruments and clinical records.

Results

The main results of this thesis are presented as the findings of three studies. In our cohort, 73% of PD patients had pain. Sixty-three percent had musculoskeletal pain, 27% had dystonic pain, 22% had central parkinsonian pain and 9% had radicular/neuropathic pain. No patient had akathisia. In 32% of the patients, the pain appeared before the motor symptoms. Pain had a median duration of 5 years and 78% of the patients had pain for more than 1 year. In 63% of the patients the pain was constant, in 28% it was intermittent, and in 9% it was sporadic. In PD patients with pain, there is a greater severity of motor symptoms with more comorbidities, more anxiety, pathological gambling, and a higher dose of antiparkinsonian drugs. PD patients with central parkinsonian pain were younger and had earlier disease onset, greater non-axial motor symptom severity in *on*, fewer comorbidities and more pain-related disability. The odds of having sleep disturbances were higher among patients with central parkinsonian pain. No differences were found in the frequency of anxiety and depression in PD patients with central parkinsonian relative to PD patients without pain or with non-central parkinsonian pain. PD patients with central parkinsonian pain had better cognitive performance in a measure of executive functions but reported more compulsive behaviors and had more current smoking habits than those without pain or with non-central parkinsonian pain. PD patients with central parkinsonian pain reported greater pain relief with antiparkinsonian medication.

Conclusion

This thesis provides an encompassing and novel approach to pain in PD. Our research indicates that pain in PD is a common and heterogeneous non-motor symptom. Central parkinsonian pain is unique in PD and has distinct demographic and clinical features. Central parkinsonian pain should be considered a relevant symptom in PD deserving special attention. The Park pain subtype can be characterized clinically by the presence of central parkinsonian pain in a younger PD patient with earlier disease onset, more severe non-axial symptoms, greater preservation of executive functions, more sleep disturbances, more compulsive behaviors (punding, hobbyism, walkabout, or hoarding), more current smoking habits, and important pain-related disability. PD patients with central parkinsonian pain had greater pain relief with optimization of antiparkinsonian medication.

The research that constitutes this PhD thesis is expected to provide an important scientific impetus and interest in the study of central parkinsonian pain. In the future, it will be essential to improve the strategies for diagnosis and evaluation of pain in PD with a standard assessment protocol to prevent and treat central parkinsonian pain in PD.

Key Words: Parkinson's disease, non-motor symptom, central parkinsonian pain, Park pain subtype

Resumo

Introdução

Classicamente, a doença de Parkinson (DP) foi descrita como uma doença com sintomas motores sendo a bradicinesia, tremor em repouso, rigidez e instabilidade postural os sintomas cardinais. Atualmente, a DP é reconhecida como uma doença complexa que também inclui sintomas não-motores, como distúrbios neuropsiquiátricos, distúrbios do sono, disfunção autonómica ou distúrbios sensoriais. A DP tem apresentação e progressão diversas e foi proposto que existem diferentes subtipos de DP.

A dor é um sintoma não-motor heterogéneo e incapacitante na DP, com uma prevalência que pode atingir os 85% dos doentes com DP. O diagnóstico da dor e a distinção dos diferentes subtipos de dor é essencial na avaliação da dor na DP. Os diferentes subtipos de dor, segundo a classificação de Ford, são distintos uns dos outros e a dor parkinsónica central parece resultar exclusivamente da DP. Atualmente os fatores de risco para dor parkinsónica central na DP ainda não estão totalmente estabelecidos. A fisiopatologia da dor na DP ainda não é completamente conhecida, mas estudos clínicos, neurofisiológicos e de imagem funcional mostraram alterações no processamento e interpretação dos estímulos álgicos em doentes com DP. O processo neurodegenerativo que ocorre na DP afeta estruturas e vias relacionadas com a dor em vários níveis do sistema nervoso incluindo alterações nas vias e estruturas dopaminérgicas e não-dopaminérgicas. A maioria dos doentes com DP não recebe tratamento para dor e as características desse tratamento ainda não estão completamente estabelecidas.

As características da dor parkinsónica central na DP, a sua relação com sintomas motores e outros sintomas não-motores, e as características definidoras do subtipo *Park pain* permanecem em grande parte desconhecidos.

Objetivos

O trabalho de investigação que constitui esta tese de doutoramento teve como principais objetivos: determinar a prevalência e características da dor e dos seus subtipos na DP; investigar a relação entre a dor parkinsónica central e as

características demográficas e clínicas na DP; explorar a relação entre a dor, a dor parkinsónica central e outros sintomas não-motores; e efetuar uma caracterização clínica do subtipo *Park pain*.

Participantes e métodos

Para atingir os objetivos deste projeto de investigação, realizámos um estudo observacional em 292 doentes com DP da Consulta de Doenças do Movimento do Centro Hospitalar e Universitário do Porto. Os doentes foram avaliados nos estados *off* e *on* e foram recolhidos múltiplos dados com base numa avaliação clínica, na aplicação de instrumentos validados e nos registos clínicos.

Resultados

Os principais resultados desta tese baseiam-se nos resultados de três estudos publicados. Na nossa coorte, 73% (n=212) dos doentes com DP apresentavam dor. Sessenta e três por cento tinham dor músculo-esquelética, 27% tinham dor distónica, 22% tinham dor parkinsónica central e 9% tinham dor radicular/neuropática. Em 32% dos doentes a dor apareceu antes dos sintomas motores. A dor tinha uma duração média de 5 anos e 78% dos doentes tinham dor há mais de 1 ano. Em 63% dos doentes a dor era constante, em 28% era intermitente e em 9% era esporádica. Nos doentes com DP e dor há uma maior gravidade dos sintomas motores, com mais comorbilidades, maior ansiedade, jogo patológico, e uma dose mais elevada de medicamentos antiparkinsónicos.

Os doentes com dor parkinsónica central são mais jovens, iniciam a doença mais cedo, apresentam maior gravidade dos sintomas motores não-axiais em *on*, menos comorbilidades e maior incapacidade devido à dor. A probabilidade de ter perturbações do sono foi mais elevada entre os doentes com dor parkinsónica central. Não foram encontradas diferenças na frequência de ansiedade e depressão entre os doentes com dor parkinsónica central e doentes sem dor ou com dor parkinsónica não-central. Doentes com dor parkinsónica central tiveram um melhor desempenho nas avaliações das funções executivas, mas demonstraram mais comportamentos compulsivos e tinham mais hábitos tabágicos

que os doentes sem dor ou com dor parkinsónica não-central. Os doentes com dor parkinsónica central tiveram maior alívio da dor com a medicação antiparkinsónica.

Conclusão

Esta tese de doutoramento proporciona uma abordagem completa e original da dor na DP. A nossa investigação indica que a dor na DP é um sintoma não-motor comum e heterogéneo. A dor parkinsónica central é uma característica única da DP e tem características demográficas e clínicas distintas. A dor parkinsónica central deve ser considerada um sintoma relevante na DP e que merece especial atenção. O subtipo *Park pain* da DP é clinicamente caracterizado pela presença de dor parkinsónica central, num doente mais jovem, com início mais precoce da DP, com sintomas não-axiais mais graves, com maior preservação das funções executivas, mais distúrbios do sono, mais perturbação do controlo dos impulsos e outros comportamentos (*punding*, *hobbyism*, *walkabout* ou *hoarding*), mais hábitos tabágicos e uma importante incapacidade relacionada com a dor. Os doentes com DP e dor central parkinsónica têm um maior alívio da dor com a otimização da medicação antiparkinsónica independentemente do estado motor.

Espera-se que o trabalho de investigação que constitui esta tese de doutoramento dê um importante impulso científico e aumente o interesse no estudo da dor parkinsónica central. Para o futuro, é essencial estabelecer um protocolo de avaliação da dor na DP e desenvolver estratégias para a prevenção e tratamento da dor parkinsónica central

Palavras-chave: doença de Parkinson, sintoma não-motor, dor parkinsónica central, *Park pain* subtipo

Abbreviations and acronyms

α-syn	α-synuclein
BPI	Brief Pain Inventory
CHUPorto	Centro Hospitalar Universitário do Porto
COMT	Catecol-O-Metiltransferase
DBS	Deep Brain Stimulation
DBS-STN	Deep Brain Stimulation- Subthalamic Nucleus
DRS	Dementia Rating Scale
fMRI	Functional Magnetic Resonance Imaging
FOG-Q	Freezing of Gait Questionnaire
BG	Basal Ganglia
GPi	*Globus Pallidus* Internal
HADS	Hospital Anxiety and Depression Scale
HRQL	Health-Related Quality of Life
H&Y	Hoehn & Yahr
IASP	International Association for the Study of Pain
ICDs	Impulse Control Disorders
ICDs-RD	Impulse Control Disorders - Related Disorder
LB	Lewy Bodies
LED	Levodopa Equivalent Dose
LEP	Laser Evoked Potentials
LRRK2	Leucine-rich Repeat Kinase 2
MAO-B	Monoaminoxidase-B
MDS	Movement Disorder Society
MRI	Magnetic Resonance Imaging
PD	Parkinson's Disease
PDI	Pain Disability Index
PET	Positron Emission Tomography
RBD	REM Behavior Disorder
REM	Rapid Eyes Movement
S&E	Schwab and England Independence Scale

SN	Substantia Nigra
SNc	Substantia Nigra pars compacta
SPSS	Statistical Package for the Social Sciences
STN	Subthalamic Nucleus
STN-DBS	Subthalamic Nucleus - Deep Brain Stimulation
UKPDSBB	United Kingdom Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's Disease Rating Scale

CHAPTER I | Introduction

Introduction

Parkinson's disease

Introduction

Classically, Parkinson's disease (PD) has been described as a disease with motor symptoms. Bradykinesia, tremor at rest, rigidity, and postural instability are the cardinal symptoms[1]. Previously, PD pathophysiology was considered to be restricted to the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), and its symptomatic treatment focused on dopaminergic replacement strategies[1].

Currently, PD is recognized as a complex disease that also includes non-motor symptoms, such as neuropsychiatric, sleep, and autonomic dysfunction or sensory disorders [2]. These symptoms occur throughout disease progression, and some of them, such as sleep disorders, hyposmia, depression, and constipation, can precede the appearance of motor symptoms by many years[3]. In most cases, this diversity of symptoms is caused by aggregation of α-synuclein (α-syn) in various areas of the central and autonomic nervous system, which can start in the gastrointestinal or olfactory system, and by the dysfunction in multiple neurotransmitters in addition to dopamine, such as acetylcholine, serotonin, and norepinephrine[4]. New pharmacological and surgical therapies cause a substantial improvement in motor symptoms, but effective treatments for most non-motor symptoms are still lacking[5].

The aim of this introductory chapter is to provide a synthesis of the literature on PD, with an emphasis on epidemiology, pathophysiology, diagnosis, non-motor symptoms, subtypes and treatment.

Epidemiology

PD is the most common neurodegenerative movement disorder and second most common neurodegenerative disease in the world's population after Alzheimer's disease[6]. The worldwide incidence varies between five and 35 new

cases per year per 100,000 persons[7]. PD is rare before 50 years of age, but its incidence increases 5–10 times between the sixth and ninth decade of life[7]. The average age of onset is 65 years old with an adjusted prevalence of 0.3%, which increases progressively with age and reaches more than 3% in people over 80 years of age[8,9]. The only study carried out in the Portuguese population showed an age-adjusted prevalence of 0.24% and an estimate of the total number of patients in Portugal of 180 per 100,000 persons[10].

Most cases of PD appear to be sporadic, but there is growing evidence that genetic factors are important in their pathogenesis, particularly in younger patients[11]. Approximately 25% of patients with sporadic PD have at least one first-degree family member with PD, and family members of PD patients have 2.3 times higher risk of developing PD[12]. In recent years, several genetic mutations have been discovered that are associated with the development of PD. It is estimated that monogenic PD, whether in the pattern of recessive or dominant inheritance, represents between 5% and 10% of PD cases[13]. The proportion of genetically defined cases increases to > 40% for those with disease onset before 30 years of age[14]. The autosomal dominant mutation leucine-rich repeat kinase 2 (LRRK2) is the most frequent known cause of PD and is associated with approximately 7% of PD cases in the Portuguese population[15]. Mutations of glucocerebrosidase (GBA) constitute an important genetic risk factor for PD; and it has been estimated that between 5% and 25% of PD patients carry GBA mutations [16]. In recent years, several genes have been associated with Parkinsonism with both atypical phenotypes and neuropathology. These findings point to the possibility of distinct diseases. Though, the current level of understanding supports the inclusion of genetic Parkinsonism in the same entity as PD[17]. Age is the only unequivocal risk factor for PD[18]. Men carry a greater risk of having PD, and the overall age-standardized incidence male-to-female ratio is estimated to be 1.46[19]. Currently, it is accepted that PD has a multifactorial etiology and results from a complex genetic–environmental interaction that modifies the risk of PD. An example of this interaction is the increased incidence of PD in individuals exposed to certain environmental factors, such as pesticides or herbicides, and traumatic injuries, and the decreased incidence in individuals who smoke, who exercise or who consume caffeine[18].

PD causes major disability and is associated with increased mortality. Years lived with disability and disability-adjusted life years due to PD increase between 1990 and 2010[20]. Mortality is not increased during the first decade after the onset of the disease, but thereafter the risk of death increases notably[21]. Considering all causes, the risk of death is about twice as high when compared to individuals of the same sex and age, particularly in patients with PD and dementia[22]. The average duration between diagnosis and death is about 15 years; however, there are patients who may live with PD for decades[23]. The increase in life expectancy and improvement in healthcare have been associated with an increase in the prevalence of PD in recent years[24] and the worldwide number of PD patients is expected to double by 2030[25].

Pathophysiology

The loss of dopaminergic neurons in the SNc and intracellular accumulation of misfolded α-syn, which is found in intra-cytoplasmatic inclusions called Lewy bodies (LB), have been considered the defining neuropathological characteristics of sporadic PD[26]. The degeneration of dopaminergic neurons translates into a decrease in dopamine levels in the basal ganglia (BG), mainly in the putamen, which causes dysregulation of connections with the thalamus and with the motor cortex leading to PD-related motor symptoms[27]. However, these neuropathological changes do not *per se* explain many of the non-motor symptoms that are present in PD. Furthermore, rare genetics forms of PD do not show LB pathology[28]. In recent years, studies have confirmed that PD is a multifocal and multi-neurotransmitter disease[26,29]. Several studies have documented the existence of α-syn in multiple areas of the autonomic nervous system, enteric nervous system, retina, skin, or submandibular glands[30]. Non-motor symptoms, such as cognitive, sensorial, or autonomic dysfunction are seen and are caused by the attainment of extra-nigral structures and changes in non-dopaminergic systems[31]. In his seminal study, Braak suggests that PD is a disease caused by the formation of LB in the olfactory bulb and in the dorsal motor nucleus of the vagus nerve with subsequent caudo-rostral cell-to-cell (prion-like) propagation[32]. This propagation reaches the midbrain, preferentially the dopaminergic neurons of SNc, and later the neocortical

structures[32]. In this model, DP is pathologically characterized by six stages[32]. The initial stage and stages 1 and 2 are characterized by disrupting structures in the spinal and the olfactory bulbs with the appearance of some non-motor symptoms (such as hyposmia); the intermediate stages, 3 and 4, are characterized by the degeneration of SNc and the appearance of motor symptoms, and the final stages, 5 and 6, are characterized by neocortex disruption, in which non-motor symptoms (such as dementia) predominate[32]. This hypothesis is corroborated by neuropathological studies showing significant neuronal loss in SNc of about 60% in the early stages of PD, indicating that the beginning of this neurodegeneration starts long before the onset of motor symptoms[33,34]. Recent studies have shown the presence of abnormal α-syn in the mucosa of the colon, stomach, and especially in the ileocecal appendix years before the onset of motor symptoms or in the initial stage of the disease and that truncal vagotomy and appendectomy may be associated with a decrease in risk of PD or later onset of the disease[35-40]. These findings suggest that the abnormal α-syn may have its origin in the gastrointestinal system, which later spreads through the vagus nerve with a predictable topographic pattern. Years after the model was published, Braak and colleagues proposed that sporadic PD starts in two places, in the neurons of the nasal cavity and intestine, and they named it the dual-hit hypothesis[41,42]. Braak's model of the spatial-temporal spread of α-syn in PD is supported by several *in vitro*, *in vivo*, and clinical studies; however, there are questions about this model's accuracy for describing PD progression in some PD patients[43,44]. For example, neuropathological studies have shown the absence of LB pathology in some patients with PD with a known genetic cause, such as mutations in the LRRK2 and the parkin genes[28,45]. Some authors argue that the Braak model is more appropriate for explaining the onset and progression of PD in younger patients with a long duration of the disease[46].

Several nuclei and non-dopaminergic systems, such as the locus coeruleus, raphe area, or autonomic system, are affected in PD and cause multiple neurotransmission system dysfunction[31]. Dementia in PD is accompanied by a decrease in cortical cholinergic markers and there is evidence that one of the causes of PD may be a decrease in noradrenergic transmission from the locus coeruleus to

the cortical regions[47,48]. The raphe area is involved in the serotonergic system and its neurodegeneration may be associated with depression in PD[49].

The pathogenesis in PD is not yet fully understood, but it is considered that the interaction between genetic and environmental factors causes a set of changes, such as neuroinflammation, changes in protein processing, mitochondrial changes or oxidative stress, which lead to death, of vulnerable cells[32].

Clinical symptoms

Clinically PD is characterized by motor and non-motor symptoms. The four cardinal motor symptoms of PD are tremor, rigidity, bradykinesia, and postural instability[50]. Secondary motor symptoms include a decrease in blink rate, hypomimia, hypophonia, diminished arm swing and/or difficulty turning over in bed[51]. As PD advances other motor symptoms occur, such as dyskinesias or dystonia, and motor fluctuations, with *off* and *on* periods[51].

In the last few years, there has been increasing recognition of the importance of non-motor symptoms in PD[31]. Some of these symptoms can precede the motor symptoms by several years, prodromal stage[52]. With progression of the disease, the non-motor symptoms start to dominate the clinical picture and are the main determinants of quality of life and institutionalization[53]. The impact from non-motor symptoms is often greater than that of motor symptoms, but, unfortunately, non-motor symptoms are often underrecognized[51]. Non-motor symptoms of PD can be divided into different categories: (1) sensory disorders (pain, olfactory deficits, visual disturbances and somatosensory disturbances); (2) neuropsychiatric disorders (anxiety, depression, apathy, fatigue, impulse control disorders [ICDs], psychosis, cognitive deficits, and dementia); and (3) autonomic disorders (bladder, gastrointestinal dysfunction and cardiovascular dysfunction) and sleep disorders[31]. Most PD patients have several non-motor symptoms, and the average number of non-motor symptoms per patient varies from 4 to 19[54]. Non-motor symptoms can also fluctuate and the non-motor fluctuations have been classified into autonomic, sensory, and cognitive subtypes[55]. Non-motor fluctuations usually manifest as anxiety, pain, fatigue, depression, clouded mind, and/or drenching sweats. These

can occur exclusively or worsen during *off* periods or present during *on* periods, for example, euphoria may occur exclusively during *on* periods[56].

Due to the research work included in this thesis, the sleep disturbances, depression, anxiety and impulse control disorders in PD will be reviewed in greater detail.

Sleep disturbances are a common disabling non-motor symptom in PD, which may interfere with quality of life, with a prevalence that varies greatly from 40% to 90%[57]. Rapid eyes movement (REM) Behavior Disorder (RBD) is a parasomnia characterized by the loss of atonia that normally occurs during REM sleep that leads to the occurrence of vigorous movements and vocalizations as if the patients are experiencing their dreams[58]. Some patients may experience severe trauma, such as falling out of bed or traumatizing your companions while sleeping[58]. The prevalence in tertiary centers as confirmed by polysomnography can vary between 40% and 45% in patients with established PD and about 30% in *de novo* PD patients[59-61]. Recently, it has been shown that patients with spontaneous RBD may develop PD or other alpha-synucleinopathy decades after its appearance[58]. The occurrence of RBD before motor symptoms, have younger onset of PD and more severe manifestations of the disease[62]. A short interval between RBD and motor manifestations is associated with an increased risk of cognitive decline[63]. The most common form of insomnia in PD is fragmented sleep, which can have multiple causes: (1) rigidity and nocturnal bradykinesia, (2) dystonia, (3) nocturia, (4) pain, (5) the effect of medications and/or (6) periodic leg movements[64]. Restless leg syndrome is also more common in PD and can occur in a quarter of PD patients[65]. Excessive daytime sleepiness and, occasionally, sleep attacks are also common[66,67]. Sleep attacks are often associated with the use of dopaminergic agonists[68]. The association between poor sleep quality and depression and anxiety has been well established[69]. There is also evidence that common sleep problems, such as sleep-onset insomnia and sleep-maintenance insomnia, may be associated with motor symptoms (such as nocturnal akinesia) and other non-motor symptoms (such as nocturia and hallucinations)[70,71].

Depression is the most common psychiatric disorder in PD, affecting about 40% of patients[72,73]. Depression can be the first symptom of the disease[72,73] and it

has been linked to disease duration, severity of motor symptoms, fluctuations, and dosage of dopaminergic drugs[74]. The diagnosis of depression in PD patients is difficult because motor characteristics, such as bradykinesia or facial expression, and somatic characteristics, such as sleep disorders or inability to concentrate, are common in depressed patients and even in those who are not depressed[75]. Commonly in depressed patients with PD, sadness, anhedonia, and loss of interest in usual activities dominate the clinical picture[75]. The occurrence of suicide in PD is similar to that of the general population[76].

Anxiety occurs in about 30% of PD patients[77]. Various types of anxiety have been described in PD with generalized anxiety disorder and social phobia being the most common[77]. Anxiety and depression can occur concurrently in the same patient and are often associated with fluctuations in the disease with or without motor manifestations[75,78].

ICDs are defined as a failure to resist an impulse, temptation, or compulsion to pursue certain reward-based activities and make poorly informed decisions without the insight with respect to potential personal and interpersonal consequences that arise from repetitive participation in these activities[79]. ICDs have an important impact on the quality of life of both PD patients and their caregivers and adversely affect interpersonal relationships, occupational functioning, and finances. The ICDs have been sub-classified into two groups: (1) ICDs and (2) ICD-related disorder (ICDs-RD)[80,81]. The four majors classical ICDs include pathological gambling, hypersexuality, compulsive buying, and binge eating[80]. The spectrum of ICDs-RD includes punding, hobbyism, walkabout, hoarding, and compulsive medication use[80]. It has been hypothesized that both ICDs and ICDs-RD are related to dysregulation or inappropriate regulation of the reward pathways in the mesocorticolimbic network[82]. The prevalence of ICDs (including ICDs-RD) in the general population varies between 0.2 and 5.3%[80]. There are few studies on the epidemiology of ICDs in patients with PD but the prevalence seems to be much higher[83]. There are reports of approximately 20% in newly diagnosed untreated PD patients[84] or in the early stages of PD patients (for example, within 3.5 years of diagnosis) have ICDs[85]. Certain risk factors have been identified in PD patients for the development of ICDs, including treatment-related, predominantly dopamine

agonists, which is the major risk factor for ICDs along with demographic factors (such as young age, male gender), genetic factors, depression, apathy, RBD, and disease-specific factors, such as the presence of motor complications[79,86]. Currently there is no effective treatment for ICDs, and the best strategy is to identify patients at higher risk for ICDs development and set up a preventive approach (for example, avoiding dopamine agonists)[87].

Diagnosis

The diagnosis of PD remains clinical and is based on the clinician's ability to recognize symptoms and characteristic signs of the disease[88]. To date, no diagnostic test has been developed to distinguish, in living patients, PD from other forms of parkinsonism. The neuropathological examination remains the gold standard for the definitive diagnosis of PD although standard pathological criteria for PD have not yet been defined[89]. PD is an extremely heterogeneous disease in its presentation and evolution[90]. In the early stages of the disease, diagnosis becomes a challenge and can be wrong in almost a quarter of patients even in specialized centers[91].

In order to increase the accuracy of PD diagnosis clinical diagnostic criteria were presented over time. In 1992, Hughes et al. published a clinical–pathological correlation study in 100 patients who had been clinically diagnosed with PD, but only 74 had neuropathological confirmation [92]. Based on this study, they proposed criteria for the clinical diagnosis of PD that became known as the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria[92]. In summary, the UKPDSBB criteria are applied in three steps: (1) definition of parkinsonian syndrome (bradykinesia associated with tremor at rest, or rigidity, or postural instability); (2) exclusion criteria (such as treatment with neuroleptics; occurrence of signs suggestive of atypical parkinsonian syndromes, such as dysautonomia or dementia at an early stage of the disease; absence of response to high doses of levodopa); and (3) at least three support criteria (such as unilateral onset, persistent asymmetry, progressive condition, excellent response to levodopa, onset of levodopa-induced dyskinesia)[92]. These have been the most frequently used criteria in PD studies in the last decades. These criteria do not take into account PD's non-

motor symptoms in the support criteria and only use them to exclude the diagnosis. A recent meta-analysis of 20 published studies showed that the accuracy of clinical diagnosis of PD has not improved in the last 25 years, particularly with respect to the early stages of the disease[93]. Considering only the 11 studies that had pathological confirmation of PD, the accuracy of diagnosis was about 80%, and two out of 10 patients have a wrong diagnosis of PD[93]. The strict application of the UKPDSBB diagnostic criteria is more sensitive (90.8% versus 81.3%) but less specific (34% versus 83.5%) and has lower diagnostic accuracy (82.7% versus 83.9%) than the diagnosis made by specialists in movement diseases[93]. Movement disease specialists use clinical pattern recognition methods that go beyond the diagnostic criteria[93].

Taking into account the advances in knowledge of the disease in recent years, the Movement Disorders Society (MDS) published new diagnostic criteria for PD in 2015[88]. The authors of these revised criteria consider that the diagnosis of PD performed by a movement disease specialist remains the gold standard for diagnosis in life[88]. The new criteria were developed to mimic the diagnostic process performed by specialists in movement diseases. To apply the criteria, two steps are considered: (1) diagnosis of parkinsonian syndrome and (2) determine whether parkinsonism is due to PD. Parkinsonism is defined by the presence of bradykinesia associated with tremor at rest or rigidity. In order to determine whether parkinsonism is due to PD, it is necessary to establish several parameters: (1) absence of absolute exclusion criteria (such as unequivocal cerebellar signs, supranuclear palsy of the lower vertical gaze, parkinsonism restricted to the lower limbs for more than three years, absence of response to high dose levodopa, and others) and (2) warning signs (such as rapid progression of gait difficulties, recurrent falls, absence of common non-motor characteristics after five years of illness, symmetrical parkinsonism, and others) if present, must be balanced by the presence of support criteria (such as clear benefit from levodopa, presence of levodopa-induced dyskinesias, and other factors)[88]. After applying the criteria, a diagnosis of PD can be established with two levels of certainty: (1) clinically established (absence of absolute exclusion criteria, at least two support criteria and absence of warnings

signs) or (2) clinically probable (absence of absolute exclusion criteria and the presence of warning signs counterbalanced by support criteria)[88].

The absence of non-motor symptoms after five years of disease duration is considered an alert factor for the diagnosis of PD[88]. Despite being a conservative criterion due to the requirement for five years of evolution, it is justified because there are patients with PD who have predominantly motor and some patients with PD and without LB (such as PD patients with parkin mutation) have less non-motor symptoms[94,95].

In summary, motor symptoms maintain their central and essential role for the diagnosis of PD, but for the first time, relevance is also given to non-motor symptoms.

Clinical evolution

In the clinical phase of PD, it is difficult to accurately predict disease progression, and it is usual to say that each PD patient develops his own form of PD[96]. Though, usually PD patients have a "good" period early after diagnosis that can last from 3 to 8 years, in which the symptoms improve after treatment[51,96]. Motor fluctuations usually affect patients within 5 to 10 years after diagnosis, which is a phase of fluctuation in the effectiveness of the treatment (*on*/*off*)[96]. In the decline phase appear major motor symptoms (such as postural instability and falls) and cognitive disorders (such as dementia) that do not respond to treatment[51,96]. Non-motor symptoms become increasingly prevalent over the course of the disease and are a major determinant of the disease outcome. In one long-term study (the Sydney study) with PD patients with more than 20 years of disease, dementia was present in 83% of patients and hallucinosis was present in 74% of these patients[97]. The majority of PD patients lose autonomy in the advanced phase of the disease[98]. Patients with younger-onset of disease have more motor fluctuations and are more prone to levodopa-induced dyskinesia, while patients with older-onset disease have more cognitive dysfunction and dysautonomia[99].

Subtypes

It has been recognized that PD is highly heterogeneous, and patients with PD present and progress in different ways[100]. For this reason, it has been speculated that there are different subtypes of PD with different pathogenesis. The basis for subtyping has been the identification of the co-occurrence or clustering of clinical features in groups of patients[101]. It has been argued that subtyping PD patients at baseline would allow for more focused research into disease etiology, pathophysiology, and treatment and would allow clinicians to predict prognosis, plan treatment, and counsel patients with much more accuracy[102]. Subtyping PD has been traditionally based on motor symptoms, but recently an attempt to define different PD subtypes that take into account the non-motor symptoms[101-104]. Most recent studies use the cluster analysis, an unbiased approach that is driven by the data and is not influenced by an *a priori* hypothesis[102]. This method is different from empirical subtyping that uses an *a priori* hypothesis as a single classification factor (such as age of onset or motor symptoms)[102]. An important limitation is that the outcome of any cluster analysis depends on the variables selected for inclusion, and therefore it is important to select valid variables[104]. Sauerbier et al. performed a clinical characterization in PD patients, mainly in the early and untreated phases, and has suggested seven specific non-motor symptoms-dominant phenotypes: (1) Park cognition, (2) Park apathy, (3) Park depression/anxiety, (4) Park sleep, (5) Park fatigue, (6) Park autonomic, and (7) Park pain[103]. Specifically, Park pain clinically expresses a range of different pain syndromes that dominate the clinical picture. These patients have a higher risk of developing pain that is disproportionate to motor severity during the progression of PD[103]. The authors stated that these non-motor subtypes probably will overlap and will change throughout the course of disease with the result that at the end, several subtypes will merge[103]. Further cohort studies are required to confirm and define the specific clinical characteristics of these non-motor subtypes in addition to biomarkers and natural history[105].

Treatment

Many treatments are available for PD symptoms[5]. These include medications, surgical procedures, occupational therapy, physiotherapy, and other

support services. These therapies, namely pharmacological and surgical, cause a substantial improvement in motor symptoms. Though, effective treatments for most non-motor symptoms are still lacking[5].

Levodopa has remained the "gold standard" antiparkinsonian drug, and over time, practically all PD patients will require treatment with this agent[106]. However, its long-term use is associated with the development of disabling motor complications in about 30% of PD patients after 2 to 3 years of exposure, and in more than 50% of PD patients after five years[91]. As a rule, the majority of non-motor symptoms do not improve much after receiving levodopa[5]. Another option for monotherapy are dopamine agonists that directly stimulate dopamine D1-3 receptors. Dopamine agonists are not as effective as levodopa in reversing motor symptoms, but are associated with lower risk for dyskinesia[98]. They have longer half-lives than levodopa but also have a higher incidence of psychiatric side effects, including hallucinations and ICDs[51]. There are other drugs that are used as adjunctive therapy with levodopa: (1) catechol-*O*-methyltransferase (COMT) inhibitors reduce the breakdown of levodopa and increase the plasma half-life of levodopa, (2) monoamine oxidase B (MAO-B) inhibitors prevent levodopa degradation in the brain and limit its reuptake, and (3) amantadine, an *N*-Methyl-d-aspartic acid (NMDA) type glutamate receptor antagonist, is used to reduce motor symptoms and dyskinesias[51].

Deep brain stimulation (DBS) is currently the surgical treatment of choice in appropriately selected patients who have substantial motor complications when optimized medical treatment has failed in treating their motor symptoms[98]. DBS is based on the use of a chronic, high-frequency direct electrical current to a target that can be the subthalamic nucleus (STN) or the internal globus pallidus (GPi). DBS exerts its therapeutic effects by dissociating input and output signals in the stimulated target and disrupting the abnormal information flow through the cortico-BG loop[107]. Careful patient selection is essential for the success of DBS and it should be performed by a multidisciplinary team experience in DBS following the Core Assessment Program for Surgical Interventional Therapies in PD (CAPSIT-PD)[108]. DBS is a complex therapy that requires a high level of expertise for adjusting postoperative stimulation and drug therapy[109].

PD patients in the early stages of disease should be referred to a physiotherapist for assessment and education and advice, including information about physical activity[110]. PD-specific occupational therapy in addition to speech and language therapy are indicated for people who are having difficulties with activities of daily living but also early on with the aim of prevention of these difficulties[111]. There is growing information with respect to palliative care for people with PD, and their family members and/or caregivers (as appropriate) should be offered opportunities to discuss the prognosis of their condition[110]. These discussions should promote people's priorities, shared decision-making, and patient-centered care[110].

Pain in Parkinson's Disease

Introduction

Pain is a frequent feature of many neurological disorders[112]. It is a common, disabling and heterogeneous non-motor symptom in PD[113-116]. Despite the fact that more than 200 years have passed since inception of pain in PD, pain remains an underestimated and underdiagnosed symptom in PD[116]. The characteristics of pain in PD, its predictors, the relationship with other non-motor symptoms and the treatment remain largely unknown[116-119].

The aim of this chapter is to provide a review of current knowledge about pain in PD, with an emphasis on classification, clinical assessment, epidemiology, pathophysiology, and treatment.

Historical perspective

"*A.B., a female about forty years of age, complained of great pain in both arms, extending from the shoulder to the fingertips. She stated that she ... has not benefited by any of the medicines which had been employed...*"[120].

It is in this unique and precise way that, in 1817, James Parkinson, described the pain phenomenon in a PD patient in his seminal work "*An Essay on Shaking Palsy*"[120].

Charcot, sixty years later, also recognized the presence of sensory changes in PD that were not related to acute pain[121]. "*Paralysis agitans…is also a cruel affection, because of the unpleasant sensations which the sufferers experience. Usually, indeed, (the neuralgic cases which we have already described being excepted), they are not affected by acute pains, but by disagreeable sensations of a special order. They complain of cramps, or rather of a nearly permanent sensation of tension and traction in most of the muscles.*¨[121].

In the late nineteenth century, Gowers in his neurology textbook, "*A Manual of Diseases of the Nervous System*", describes pain in PD with special emphasis and notes that it may precede the diagnosis of PD[121]. *"A prodromal stage characterized by rheumatoid and neuralgic pains is met with or precedes the onset in rare cases…"*; *"…subjective sensations are frequent. Aching pains in the limbs, more or less rheumatic in character, are occasionally complained of in the early stage, and they may correspond with the commencing tremors."*[121].

Oppenheim, in the early twentieth century, also commented on painful PD syndromes that may occur in early PD and may worsen with disease progression[121]. *"Pain is not always present and is not usually acute. It is generally described as rheumatoid and may be an early symptom. It is seldom a marked symptom throughout the course of the disease ("forme douloureuse" of L'Hirondel)* ¨[121].

Souques, in 1921, described multiple painful syndromes in PD patients and was the first author to argue for the existence of an exclusive and singular subtype of pain in PD, "central pain"[122]."Pour moi, ces douleurs ne constituent pas un phénomène surajouté; elles appartiennent à la maladie de Parkinson…Je me demande si, dans certain cas, elles ne seraient pas d`origine centrale (médullaire et surtout cérébrale)…"[122].

More than fifty years later, in 1976, Snider et al. published an observational study in the journal *Neurology.* The study included 101 patients with PD, of which 43 had painful syndromes[123]. They hypothesized that some sensory symptoms originated in the nervous system and were manifestations of the disease itself, and not secondary to motor changes.

Marsden, in 1984, wrote a review on PD and repeatedly emphasized the importance of pain as a non-motor symptom in PD[124]. This was followed by Goetz

in 1986, who reported the first systematic evaluation of pain in PD (n = 95)[125]. In the same year, Quinn et al. published an article in *The Lancet* with the suggestive title “Painful Parkinson's Disease” describing ten clinical cases of patients with PD and pain[126].

In 1995, Chudler and Dong published an important article defining the importance of BG in pain[127].

Defazio et al. (2008) conducted the first observational case-control study and showed that pain should be considered a non-motor symptom in PD[128]. And finally, in 2010, Ford established a clinical classification for PD pain based on the etiology of pain and its association with motor symptoms[119].

Patient perspective

In two interesting self-assessment studies on symptoms in PD, pain is one of the symptoms that most affects patients at any stage of the disease [129,130]. In a survey of 75 PD patients and pain appeared as the third symptom (13%), affecting the patients the most immediately after tremors and bradykinesia[129]. In a study, 265 PD patients were asked about the three symptoms that they found to be the most troublesome during the previous six months[130]. In patients with fewer than six years of disease duration (n=92), pain was the fourth most commonly reported symptom (25%), just behind bradykinesia, tremors and rigidity. It was the main symptom for approximately 10% of the patients. In patients with six or more years of disease duration (n=173), pain was reported as the sixth most mentioned symptom (16%) and was the main symptom for about 6% of the patients.

Interestingly, about 40% of PD patients with pain did not report it to their neurologists, possibly because they believed pain was not associated with PD[131].

Pain decreases the quality of life of PD patients[132-136]. A case-control study compares health-related quality of life (HRQL) and pain in PD patients (n = 57) and controls (n = 95)[133]. They concluded that there is a decrease in HRQL in patients with pain and PD. The same results came from another study, who noted a worsening of pain and quality of life as the disease progressed[132]. Pain may have a greater impact on patients’ quality of life than motor symptoms. One study showed that pain had an important impact on patients' quality of life, which was sometimes

greater than their motor symptoms[134]. Other studies showed that chronic pain is the main predictor of quality of life in PD patients[135]. One study evaluated the different pain subtypes in PD and the conclusion was that they were all associated with a poor quality of life[136]. Pain is also known interfere with the performance of activities of daily living and work in most PD patients[137,138].

Classification and assessment

Pain is defined by the International Association for the Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage[139]. Pain is a difficult symptom to classify and evaluate because, as a construct, it is a subjective experience that depends on a personal interpretation that is based on past experiences and expectations, and there is a lack of objective measures.

The main reasons for underdiagnosing and undertreating pain in PD are the difficulties in its definition and characterization[116]. Pain in PD is highly heterogeneous and, therefore, its classification is useful to identify the underlying pathophysiology and for establishing the best treatment in clinical practice[140]. Multiple syndromic classifications of pain in PD have been proposed[141], and some have tried to dichotomize pain in PD as nociceptive or neuropathic[142], PD-related or not PD-related[143], and primary or secondary[123]. Other authors have also suggested that pain classification in PD should be based on the classification proposed by IASP, which attempts to distinguish nociceptive pain directly or indirectly caused by motor symptoms (e.g., dystonia or painful dyskinesias) from neuropathic pain[144,145].

Among the different classifications for pain in PD the most accepted and worldly used is the one proposed by Ford[119]. This classification is based on the etiology of pain and its association with motor symptoms. According to Ford's framework, PD pain can be classified into five subtypes: musculoskeletal pain, dystonic pain, radicular/neuropathic pain, central or primary pain, and akathisia[119] (Table 1).

Table 1. Clinical classification of painful or unpleasant sensations in PD

Category by description	Clinical features
Musculoskeletal	Aching, cramping, arthralgic, myalgic sensations in joints, and muscles; Associated findings may include muscle tenderness, arthritic changes, skeletal deformity, limited joint mobility, postural abnormalities, and antalgic gait; May be exacerbated by parkinsonian rigidity, stiffness, and immobility, and relieved by mobility; May fluctuate with medication dosing, and improve with levodopa
Dystonic	Associated with sustained twisting movements and postures; Muscular contractions often very forceful and painful; Dystonia may involve any limb or extremity, as well as facial and pharyngeal musculature; May fluctuate closely with medication dosing: early morning dystonia, off dystonia, beginning-of-dose and end-of-dose dystonia, peak dose dystonia
Radicular/neuropathic	Pain in a root or nerve territory, associated with motor or sensory signs of nerve or root entrapment
Central or primary pain	Burning, tingling, formication, ‘‘neuropathic’’ sensations, often relentless and bizarre in quality, not confined to root or nerve territory; Pain may have an autonomic character, with visceral sensations or dyspnea, and vary in parallel with the medication cycle as a non-motor fluctuation; Not explained by rigidity, dystonia, musculoskeletal or internal lesion
Akathisia	Subjective sense of restlessness, often accompanied by an urge to move; May fluctuate with medication effect, and improve with levodopa

From: Ford, B., *Pain in Parkinson's disease.* Mov Disord, 2010. 25 Suppl 1: p. S98-103.[119]

These different subtypes of PD pain are not mutually exclusive and may combine in multiple ways simultaneously or at different times throughout the duration of the disease (e.g., central pain can be more prominent at the onset of the disease and dystonic pain at a later stage)[119], may be related to the disease itself, and not the result of dystonia, rigidity, or have a musculoskeletal cause. [119,146,147]. Central pain was first described in 1921 by Souques[122]. Recently, Cury et al. proposed a change in the designation of this pain subtype[148]. These authors argue that the term "central" is nonspecific, evokes central neuropathic pain, which is a different clinical entity. For these reasons, they propose a new term "central parkinsonian pain" to avoid confusion or misinterpretation. Henceforth we will assume this designation[148].

Of the various pain subtypes in PD, central parkinsonian pain is the most interesting to study because it is the only subtype that is a direct consequence of the PD. Central parkinsonian pain may be the core and main feature of Park pain[103]. Central parkinsonian pain results from abnormal painful information processing; it is not related to a lesion in the peripheral nervous system and does not fulfill the current criteria for central neuropathic pain[140]. It has the most disabling of all subtypes of pain and is often described as a diffuse burning, bizarre or an unexplained sensation[135,149]. It is poorly characterized and difficult to describe not only by patients but also by neurologists[135,149].

This subtype of pain may have an autonomic character, with visceral sensations or dyspnea and may vary in parallel with the medication cycle as a non-motor fluctuation. Central parkinsonian pain may have a semiological overlap with other subtypes of pain[149]. For example, Mylius et al. recently described a pain syndrome associated with dopamine agonist withdrawal syndrome that is difficult to differentiate from central parkinsonian pain, and in this case one of the key features to distinguish is the relationship between symptom improvement and the restart of dopamine agonist[150]. To overcome these limitations, in clinical practice pain assessment in PD patients is based on an exhaustive clinical evaluation that includes the history of pain, neurological examination, and, if necessary, complementary diagnostic tests. In the history of pain, particular attention should be paid to the relationship between pain and the onset of PD, motor symptoms (e.g.,

laterality, motor fluctuations or dyskinesias), other non-motor symptoms, and antiparkinsonian medication. The syndromic pain classification, according to the Ford classification, is based on the best clinical judgment.

In addition to the Ford classification, the use in clinical practice of pain scales or questionnaires is fundamental for the characterization of pain in its different dimensions. The Brief Pain Inventory (BPI)[151] and the Pain Disability Index (PDI)[151] may be used to assess pain intensity and interference with daily activities. More general scales may also be used that include pain assessment, such as Medical Outcomes Study 36-Item Short Form[152] or the Unified Parkinson's Disease Rating Scale (UPDRS)[153].

In summary, clinical assessment together with dedicated scales remain the mainstay in the study of PD pain. The diagnosis and distinction of different pain subtypes in PD is essential in the evaluation of PD pain. The different pain subtypes, defined by Ford's syndromic classification, are distinct from each other. Central parkinsonian pain seems to result exclusively from PD.

Epidemiology

Pain is one of the most common non-motor symptoms in PD and several studies have shown that pain is more prevalent in PD patients than in controls[117,128,154]. The estimated prevalence of pain in PD varies between 40% and 85% with a weighted mean prevalence of 67.6%[113]. Considering the different subtypes of PD pain, musculoskeletal pain is the most common subtype (between 45% and 70%), followed by dystonic pain (between 8% and 40%), radicular or neuropathic pain (between 5% and 20%) and central parkinsonian pain (between 4% and 16%)[155,156]. The prevalence of central parkinsonian pain in most studies is probably underestimated because the diagnostic criteria are not well defined, and its features can overlap with those of dystonic and musculoskeletal pain. In a recent British study, central parkinsonian pain had a prevalence of about 27% in early-stage PD patients[134]. These variations in prevalence can be explained by the use of different criteria for pain classification and the lack of objective outcome measures. From 30% to 70% of PD patients reported more than one pain subtype and also had different combinations of pain subtypes simultaneously[117,132].

Another way to study the prevalence of pain in PD is to evaluate the use of analgesics by PD patients. Brefel-Courbon et al. conducted an interesting pharmacoepidemiological study among 11,000 PD patients, showing that patients with PD had more analgesic prescriptions than the general population (82% versus 77%) and that the prescription of analgesics for chronic use, like opiates, was also higher in PD patients (33% versus 20%)[157].

Azevedo et al. conducted an observational study in the Portuguese population showing a prevalence of chronic pain of 37%[158], but no studies on the prevalence of pain in Portuguese patients have yet been published.

Pain may also occur years before the diagnosis of PD. In a study of 433 patients with PD, reported that approximately 21% of patients had only non-motor symptoms in the prodromal phase, and pain was the most frequent (15%)[159]. In another study, about one-third of PD patients had pain before the diagnosis of PD[128]. A study reported the presence and onset of non-motor symptoms in 109 newly diagnosed untreated PD patients and found unexplained pain in 20% of PD patients in a time period of 2 to 10 years before the onset of motor symptoms[160]. And another study reported that subjects with moderate to severe pain had a higher risk of developing PD with a hazard ratio of 2.88[161].

Pain affects all body parts, including the trunk, back, shoulders, upper and lower limbs. Back pain is nearly three times more prevalent and more intense in PD patients than in the general population[128]. PD patients may report non-traumatic shoulder pain that precedes motor symptoms by several years or as a presenting symptom of the disease, and many are initially evaluated by orthopedists[162,163]. Pain was associated with an increased incidence of frozen shoulder and with severity of akinesia, particularly in the early stages of the disease[142]. In PD patients unusual pain syndromes may involve the oral area, abdomen, epigastrium, pelvis, rectum, and genitalia[164].

Risk factors

There are multiple factors that may influence the presence and intensity of pain in PD. Currently, however, the risk factors for pain in PD are not fully established and studies show varying results. It should be noted that most studies

on risk factors have not evaluated the different subtypes of pain in PD, namely central parkinsonian pain, which may explain the inconsistent results between the different studies.

Demographic

Some studies have shown a lower mean age of patients with PD and pain [125,143] but other studies have not shown this relationship[128,165].

Some studies have shown a higher frequency of pain in women with PD [117,164,166], but these data have not been confirmed by other studies[125,128,167].

Motor symptoms and antiparkinsonian medication

Motor symptoms (e.g., dystonia or rigidity) can cause or worsen pain in PD[117]. However, since 1995, with the studies of Chudler and Dong, it is understood that the pain mechanism in PD are not fully explained by the intensity of motor symptoms[127]. Some research has shown an association between pain and severity of the disease and motor complication[2], while other studies have not identified such relationship[117,128,168]. Some studies found that pain in PD was associated only with bradykinesia[137] while other studies showed an association only with rigidity[135,138]. Still others show that pain is related to postural changes[166,169]. Pain can occur with greater intensity on the side that the first motor symptoms occur[170], but it can also occur on the side not yet affected by motor symptoms[167]. Pain intensity may vary during the day, unrelated to motor status and may be linked to the availability of dopamine in non-motor circuits. Pain can improve with the administration of levodopa even in the absence of motor progress[167].

Pain in PD can also be associated with motor fluctuations and dyskinesias [164,166,167]. Studies have shown a significant improvement in pain with antiparkinsonian medication and an increase in pain during *off* periods[171-173]. However, one study found no relationship between pain and the number of hours in the *off* period[174].

Disease progression

Antonini et al. studied non-motor symptom progression in more than 700 PD patients and reported that pain can occur at any time during PD[175]. Pain can be

present in almost 40% of PD patients early in the course of disease[176], and research has shown that the prevalence of pain increases with disease progression[164,166]. Considering the progression of PD based on the Hoehn and Yahr (H&Y) scale, the prevalence can vary from about 50% in stage 1 to 80% in stages 4-5[164]. However, other studies have failed to demonstrate a correlation between the presence or intensity of pain and the stage or duration of the disease[117,165,177].

Comorbidities that cause pain

One of the difficulties in the study of the epidemiology of pain in PD is the age of the patients, which increases the risk of comorbidities. These conditions themselves can cause pain, e.g., muscular-skeletal deformities or arthritis[114]. In the DoPaMiP study, 450 patients with PD and 98 controls were evaluated[143]. The researchers classified chronic pain in PD patients into two groups: one group with pain related to PD (i.e., Pain-PD) and another group with pain not related to PD (i.e., Pain-Non-PD). Twenty-six percent of the patients had Pain-Non-PD (most related to osteoarticular pathology) and 39% had Pain-PD. One conclusion from this study is that patients with PD are twice as likely to suffer from chronic pain compared to controls even when adjusted for comorbidities[143]. Other studies have also shown similar results for pain in general[178], shoulder pain[179], and back pain[180].

Sleep disturbances

In general population, sleep disturbances and pain are frequent comorbidities. There is evidence from experimental and longitudinal studies that pain and sleep interact in a bidirectional manner and negatively affect each other [181]. Also, in PD studies have shown that sleep disturbances are a risk factor for pain and vice versa[118,166,182-185].

Depression and anxiety

Studies show that depression, common in PD, is a predictor of the presence of pain in PD[143,154,166], but other studies have failed to show this association[167,186]. Pain in PD can also be associated with greater anxiety[184].

Impulse Control Disorders

A recent study could not find a relationship in PD patients between ICDs and pain in PD patients[85]. Although, PD patients with central parkinsonian pain are known to be younger and it is also widely recognized that younger patients with PD are at higher risk of presenting impulse control disorders[83,187].

Genetic factors

Some preliminary studies have shown that genetic factors can contribute to pain in PD. Variants of the sodium voltage-gated channel alpha subunit 9 and fatty acid amide hydrolase genes, and polymorphisms of the COMT gene may be associated with increased susceptibility to pain in PD[188,189].

Pathophysiology of pain

The pathophysiology of pain in PD is still unclear. For a better understanding of pain in PD, it is useful to review the neurobiology of pain in non-PD populations.

Pain neurobiology

Melzack and Casey proposed three dimensions of pain that could influence each other: a discriminative-sensory dimension, which corresponds to the intensity, duration, quality, and location of nociceptive stimuli; a motivational-affective dimension, which involves an emotional and autonomic response to pain; and a cognitive-evaluative dimension, which allows the control of these two previous dimensions and is based on the patient's beliefs and previous experiences of pain[190].

The pain process most often begins in the periphery with the stimulation of specialized sensory receptors, the nociceptors[191]. Thermal or mechanical stimuli activated predominately nociceptors with myelinated fibers, Aδ, and chemical or thermal stimuli activated mostly nociceptors with unmyelinated fibers, C fibers[191,192]. The resulting nerve impulses are then transmitted to the dorsal horn of the spinal cord (or the trigeminal nucleus in the case of stimuli of the face and part of the scalp), namely to the T cells (lamina V), which have a role in transmitting the impulses to the brain centers, and to the gelatinous substance (lamina II), which has a role in

modulating the T cells[191,192]. There is also a descending pathway, which start in several brain structures and have the function of modulating and integrating pain information in the dorsal horn of the spinal cord, and use multiple neurotransmitters such as serotonin, noradrenaline, or dopamine[191,192].

The sensitivity of the dorsal horn neurons may increase or decrease due to these descending pathways and local interneurons[191]. The interaction between these different elements at spinal cord level is explained by the gate control theory of pain[193].

The brain structures that are involved in the processing of pain stimuli have been continually updated in recent years. In 2013, Garcia-Larrea and Peyron, in their seminal work, defined the concept of "pain matrix"[194]. This is a fluid system that includes several neuronal networks that are hierarchically activated by a painful stimulus and set aside as the concept of a single brain "pain center". The "nociceptive matrix" is the first-order network that receives spinothalamic projections and is related to the location, quality, and intensity of pain[194]. Damage to this matrix results in selective pain deficits. There is a second-order network that allows the transition between cortical nociception and pain awareness; and consists of neuronal structures, such as the posterior parietal lobe, prefrontal lobe, and areas of the anterior insula[194]. The activation of this neuronal network leads to modulation of attention and control of vegetative reactions but does not evoke pain. Finally, a third-order network, which includes orbitofrontal, cingulate and limbic areas, is involved in the experience, emotions, and expectation of pain[194]. Pain results from constant interaction between these three subsystems.

The concept of the "pain matrix" does not rigidly define brain structures that are exclusively dedicated to pain, because many of these structures have other neurological functions that include cognition, emotion, and motivation[194]. Some authors have defended the existence of a "salience network" that consists of an extensive neuronal network. Its main cortical structures are the anterior insula and the dorsal anterior cingulate cortex and it includes three subcortical structures, i.e., amygdala, ventral striatum, and substantia nigra[116]. In chronic pain the activity of this "salience network" is altered and seems to play a key role in the emotional dimension of pain[195].

Role of basal ganglia in pain

The BG were traditionally not associated with the processing of nociceptive stimulus or central pain. However, after the publication of the studies by Chudler and Dong in 1995, and Borsook et al. in 2010, the BG became recognized as playing an important role in the integration of pain information and in the coordination of complex motor responses that are associated with painful stimuli[127,196]. Animal and human studies have shown that neuronal activity in BG can be elicited by nociceptive stimuli[142]. Nociceptive signals reach the BG, directly and indirectly, from multiple brain structures, such as the sensorimotor cortex, posterior and medial thalamus, superior colliculus, parabrachial area, nucleus of raphe, or amygdala[127]. These brain structures are essential for the transmission and processing of the nociceptive signals and form part of the "pain matrix"[194].

Neurons in substantia nigra, striatum, and pallidum may respond selectively to nociceptive stimuli with multisensory properties, e.g., stimulus intensity, but do not have a somatotopic arrangement[127]. This suggests that BG are more important in the affective-emotional dimension of pain than in its spatial location. Animal studies have shown that substantia nigra stimulation causes nociceptive inhibition by dopaminergic activation of spinal cord neurons[197,198]. Other studies have demonstrated the importance of these neurons in coding nociceptive stimuli and in sensory discrimination[127,199]. Substantia nigra may play an important role in discriminating aspects and behavioral responses to pain[156]. The striatum receives multiple afferences from sensory structures and appears to play an important role in coordinating a behavioral response[156]. After a pain stimulus, dopamine secretion in the dorsolateral striatum has been detected, and the ventral striatum seems to be related to the emotional dimension and pain-related expectations, which, in turn, influence the subjective perception of pain intensity[156].

Role of dopamine in pain

Dopamine plays an important role in different levels of pain processing. Dopaminergic neurons from SNc, the ventral tegmental area, and the hypothalamus project into multiple brain structures that are constituents of the "pain matrix"[156]. Numerous animal studies have demonstrated the role of dopamine in the

modulation and transmission of pain[200]. Nociceptive stimuli increase the activity of mesocortical and mesolimbic neurons and cause dopamine release; increased concentration of dopamine in the nucleus accumbens after local amphetamine infusion causes analgesia in rats; and lesion of the dopaminergic terminals in the striatum increases the transmission speed of nociceptive signals[200]. In healthy adults, pain stimuli trigger the activation of dopaminergic receptors (D2) in the BG, in the dorsal nucleus of caudate, and in the putamen, as shown with the use of positron emission tomography (PET), and this activation contributes to the individual variation of pain experience at physical and emotional levels[201]. Some authors argue that the response to acute pain provokes an activation of the dopaminergic circuits, but, curiously, the response to chronic pain causes a hypodopaminergic state that is associated with motivational changes that, in turn, lead to anodynia and depression that are often related to chronic pain[202]. In the clinic, diseases that are associated with excess dopamine (e.g., schizophrenia) are characterized by pain hyposensitivity and diseases that are associated with dopamine deficiency (e.g., PD or depression) are associated with pain hypersensitivity[203].

Pathophysiology of pain in Parkinson's disease

The pathophysiology of pain in PD is not fully understood. Currently there are clinical, neurophysiological, and functional imaging studies that demonstrate alterations in the processing and interpretation of pain in PD patients[204,205].

Structural Considerations

The neurodegenerative process that occurs in PD, described earlier, affects pain-related structures and pathways at multiple levels of the nervous system: nociceptors, peripheral transmission, spinal cord, ascending pathways, and brain structures that are involved in stimuli reception, processing, and interpretation of pain[156]. These multiple structures are included in the "pain matrix" and in the "salience network"[194,206].

Studies in PD have described two phylogenetically distinct systems, the medial and the lateral systems, carry out the transmission and perception of pain impulses from the dorsal horn of the spinal cord to the brain centers of pain[192]. The

medial system, phylogenetically the oldest, is involved in the autonomic response, the cognitive and the affective dimension of pain. It is constituted by the paleospinothalamic, spinomesencephalic, spinoreticular, and spinothalamic tracts[156]. These fibers end in multiple brain structures, including the locus coeruleus (reticular formation), periaqueductal gray matter (midbrain), medial and intralaminar thalamic nucleus, parabrachial region, insula, parietal operculum, secondary somatosensory cortex, amygdala, and hippocampus[156]. The lateral system is involved in the sensitive-discriminative component of pain and provides information about the location and duration of pain. It is constituted by the spinothalamic and trigeminothalamic bundles and the dorsal horn of the spinal cord[156]. These fibers end in the lateral thalamus, primary and secondary somatosensory cortex, insula, and parietal operculum[156].

The locus coeruleus, the gigantocellular nucleus, and the bulbar raphe nucleus, constituents of the medial pain system, show α-syn accumulation even in the pre-motor states of PD[207]. These areas are involved in the inhibition of nociceptive signals at the spinal cord level and in automatic responses to pain[208]. From the lateral pain system, the denervation of the nigrostriatal system, typical of PD, increases the neuronal activity of the STN, GPi and substantia nigra[208]. The hyperactivity of these areas causes intense inhibition of the lateral thalamus that plays an important role in the central mechanisms of pain[209]. This causes a disinhibition of the spinothalamic-cortical medial pathway, which results in central pain and “positive” phenomena, such as paresthesia and allodynia, and a reduction in the capacity of the thalamus to spatial discrimination of pain, which may explain the difficulty that PD patients have in locating pain[123]. At the central nervous system, we can identify and correlate structures that are affected in PD and that simultaneously play an important role in pain, based on the six stages of Braak (Table 2)[32,200].

It should be noted that the transmission of nociceptive information from the periphery to the brain centers is modulated by multiple brainstem structures that are affected in PD and some are affected prior to substantia nigra involvement (stage 3-4), supporting the notion that pain may be a pre-motor symptom in PD.

Table 2. Correlate structures that are affected in PD and pain

		Braak Stages
Cortex	Dorsolateral prefrontal cortex	5-6
	Orbitofrontal cortex	5-6
	Insula	5-6
Mesial temporal lobe	Amygdala	4
Diencephalon	Intralaminar thalamic nucleus	4
	Hypothalamus	3-4
Brainstem	Substantia nigra	3-4
	Ventral tegmental area	3-4
	PAG	3-4
	Serotonergic nucleus of the parabrachial area	2
	Magnocellular portion of the reticular formation	2
Spinal cord	Dorsal horn nociceptive neurons	2
	Sympathetic and parasympathetic preganglionic neurons	2

PAG – *periaqueductal gray matter*
Adapted from: Braak et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiology of aging* 2003; 24(2): 197-211.[32]

Alterations in peripheral nervous system structures that are involved in the reception and transmission of pain stimuli, such as reduced density of unmyelinated nerve fibers, cutaneous denervation with loss of nerve endings or neurodegeneration of nociceptors, have also been demonstrated in PD[210-212]. Some authors argue that these changes in nociceptors and the resulting deafferentation play an important role in sensory dysfunction in PD[211]. However, the concept that skin denervation may cause generalized distal sensory axonopathy in PD still needs further investigation.

At the level of central structures, Polli et al. investigated the cortical morphological changes that may be involved in the development of pain in PD using magnetic resonance imaging (MRI)[213]. In a study with 40 PD patients (20 with pain and 20 without pain) and 15 pain-free controls, they found that PD patients with pain

had morphological changes (thinning) in several cortical areas associated with the medial and lateral pain systems, and structures involved in the emotional assessment of pain, which included the dorsolateral prefrontal cortex, orbitofrontal cortex, and posterior cingulate cortex[213]. In a recent neurophysiological study, Zambito-Marsala et al. tried to clarify the role of peripheral and central structures in pain processing in PD[147]. They concluded that abnormal processing of nociceptive stimuli occurs mainly at the central level and not at the peripheral level[147]. They also suggested that there is an imbalance in functioning between the medial and lateral pain systems and that such dissociation may explain the central genesis of pain in PD[147].

Functional Considerations

Different neurophysiological evaluations have been used to study mechanisms and dimensions of pain in PD. In these studies, various stimuli (e.g., thermal and electrical) are used to investigate pain tolerance and pain threshold[204,214,215]. Pain tolerance is defined as the minimum intensity of stimulation that is perceived as an intolerable painful sensation and assesses the cognitive and affective dimension[116]. Pain threshold is defined as the minimum intensity of stimulation to which the individual reports a change from a painless sensation to a painful sensation and assesses the sensory-discriminative dimension[116]. Methods such as the nociceptive withdrawal reflex (NWR), which consists of electrical stimulation of the sural nerve, are used to evaluate the spinal cord pain processing. The scalp laser evoked potentials (LEPs) are used for non-invasive evaluation of the functional alterations of different brain structures (e.g., insula and cingulate gyrus) to pain stimuli[116].

A systematic review and a meta-analysis of neurophysiological studies comparing response to painful stimuli between PD patients with and without medication and healthy controls has been recently published[216,217]. Sung et al. studied the pain threshold and included 22 studies within a total of 1067 participants (616 PD patients and 451 healthy controls)[216]. Most studies (15/19) showed a reduction in pain threshold (increased sensitivity to pain stimulus) in PD patients[216]. The meta-analysis revealed a significant reduction in pain threshold in PD patients

in all pain modalities, which did not occur when levodopa was administered to PD patients[216]. The authors of the study concluded that PD patients have a higher sensitivity to pain stimuli compared to healthy controls and that levodopa deficit states may contribute to hyperalgesia[216]. Thompson et al. analyzed the studies that evaluated the response to all pain stimuli[217]. They included 26 studies, with a total of 1292 participants (739 PD patients and 553 healthy controls) and reached to similar conclusions. There is evidence this hyperalgesia in PD patients may contribute to pain onset/increase, and that dopamine deficiency is a potential cause[217].

In two studies, Tinazzi et al. found changes in central pain processing in PD patients, regardless of whether or not they had pain and regardless of the affected side, and curiously found no differences between *off* and *on* stages[214,215]. They concluded that the abnormal processing of pain stimuli is independent of the clinical expression of motor symptoms in PD[32,33]. Several clinical studies have shown that pain in PD often responds to levodopa administration and that there is a dissociation between pain improvement and motor symptoms improvement[165,174,218,219]. Some patients with pain may experience dopamine dysregulation syndrome, which is characterized by self-medication and an addiction to dopaminergic drugs in excess to control motor symptoms and the discomfort related to non-motor symptoms such as pain[220,221].

Functional neuroimaging studies have contributed to a better understanding of the changes that are associated with pain in PD. Recently, two studies using functional magnetic resonance imaging (fMRI) in early pain-free PD patients were published[222,223]. Tessitore et al. investigated central pain processing in nonmedicated and pain-free PD patients[222]. They used two thermal stimuli, 41ºC and 53ºC, and compared brain structures activation in 20 nonmedicated and pain-free PD patients and 18 healthy controls[222]. In the lower temperature stimulus, 41ºC, there were no differences; however, in the more intense stimulus, 53ºC, they observed increased activation in the left somatosensory cortex, left cerebellum and right protuberance in PD patients[222]. They also found that cerebellum and brain stem activation correlated with pain intensity[222]. These authors suggest that even at an early stage of PD and in pain-free patients there is already compensatory

remodeling of pain processing pathways induced by neuropathological changes in early PD. They also hypothesized that with the evolution of the disease these alterations, become dysfunctional and later contribute to the onset of pain[222].

Tan et al. performed an fMRI study at rest and with a pain-inducing task to identify changes in pain-related brain functional connectivity[223]. When compared to controls, PD patients showed decreased functional connectivity in putamen by painful thermal stimulation, and in the resting state they showed decreased brain connectivity in the salience network and sensorimotor network[223]. They also found in PD patients decreased functional connectivity in both states between the BG and the salience network, and a dysfunction of the right frontoparietal network, an important structure in the emotional and cognitive processing of pain stimuli[223]. They concluded that BG has a fundamental role in the pathological mechanisms of pain in PD and the right frontoparietal network is dysfunctional in the early stages of PD[223]. From the same authors, another fMRI study in early drug-naïve PD patients, provided support that the superior temporal gyrus and insula are important parts of the somatosensory circuitry recruited during the period of pain. The hypoactivity of the superior temporal gyrus and insula implied that functions including affective, cognitive, and sensory discriminative processes, were disturbed in PD[224].

Brefel-Courbon et al. published studies on pain in PD using PET to evaluate brain structures that are involved in the processing and interpretation of nociceptive stimuli and the role of dopamine[205,225]. In one study, pain-free PD patients evaluated in the *off* stage showed a significant increase in cortical activation, induced by nociceptive stimuli in the ipsilateral prefrontal cortex, ipsilateral insula, and contralateral anterior cingulate, as compared with healthy controls[205]. They concluded that the sensory-discriminatory (insula) and affective-motivational (prefrontal cortex and anterior cingulate) processing of pain are changed in PD[205]. Interestingly, in the other study they found that in the *off* condition, PD patients with pain had a lower pain activation in the right prefrontal cortex and posterior insula and a higher pain activation in the right anterior cingulate cortex than pain-free patients[225].

The same group used PET to understand the effect of apomorphine on the threshold and processing of pain in PD and found no difference in brain activation

after its administration[226]. These data are not at all unexpected considering the involvement of many non-dopaminergic structures in PD and other neurotransmitters, such as noradrenaline and serotonin.

The pain-modulating descending pathways that are fundamentally serotonergic and noradrenergic are affected in PD[126]. In PD patients with pain, compared to pain-free PD patients and healthy controls, greater serotonin denervation and a reduction of a serotonin metabolite in cerebrospinal fluid has already been demonstrated[227,228]. Also, in regard to the impact of levodopa on pain, Lim et al. conducted a study to compare the change in pain sensitivity after levodopa administration between stable responders, fluctuators without dyskinesia, and dyskinetic patients, and to compare pain sensitivity between PD and healthy subjects[174]. PD patients *off* medication had a lower threshold and tolerance to pain compared to controls. After levodopa administration, dyskinetic patients experienced a large increase in pain threshold and tolerance that was absent in stable responders. Limbic and associative brain structures, which are activated in dyskinetic patients are also involved in the reward system[174]. This result may possibly explain some of the differences in levodopa's effect on pain threshold in different studies, because some studies enrolled patients with different characteristics, e.g., long disease duration or with motor complications, in the same patient group[116].

The pathophysiology of different pain subtypes in PD remains unclear. Regarding central parkinsonian pain, Schestatsky et al. carried out a neurophysiological evaluation study using thermal stimulation tests and evaluating LPE responses and laser-induced sudomotor skin responses in nine PD patients with central parkinsonian pain, nine PD patients without pain and nine healthy controls without pain[204]. In the *off* stage, PD patients with central parkinsonian pain presented higher amplitudes of the LEPs and lower habituation of sudomotor response compared to the other participants[204]. This effect was more marked on the side most affected by PD[204]. Following levodopa administration these differences disappeared or were significantly attenuated. These findings suggest an abnormal control of the effects of nociceptive stimuli on autonomic centers. The improvement with levodopa suggests that in PD patients with central pain, dysfunction may occur

in dopamine-dependent centers that are involved in autonomic function and inhibitory pain modulation.

Juri et al. proposed an original model in order to explain central parkinsonian pain[229]. This model assumed an intrastriatal amplification of sensory inputs from cortical projections owing to dopamine depletion.

In summary, it has been demonstrated that PD patient's alterations in the peripheral and central nervous system cause changes in transmission, processing, and interpretation of painful stimuli in specific brain structures and connections. A decrease in pain tolerance and threshold and abnormal pain-induced activation in cortical pain-related areas have been reported. These changes appear to be related to a dysfunction of the integrative process of pain, increased activity of medial and lateral systems, and alterations in dopaminergic and non-dopaminergic pathways.

Treatment

Multiple studies show that pain in PD is undertreated[117,165,230]. Beiske et al. found that about half of PD patients with pain were not receiving pain treatment[117]. PD patients reluctance to increase the number of drugs, fear of drug interaction, poor tolerability or unsatisfactory response to analgesics, preference for non-pharmacological approaches contribute to the undertreatment[231]. There are limitations in studying treatment of pain in PD and the main difficulties in conducting these studies have been the classification and categorization of pain, the lack of controls or comparator groups, and the difficulty in defining outcome measures[116,232]. Another difficulty of all pain studies, demonstrated in systematic reviews, is the high proportion of benefit and adverse effects of the drug that are attributed to the placebo and nocebo effects[233,234]. The difficulties in treating pain are so evident that recently a group of experts on movement disorders published a review article in which they stated that, because of lack of evidence, it is impossible to give categorical advice in the treatment of pain in PD[116].

The following sections will briefly review the latest studies on pain treatment in PD.

Pharmacological

Given the pathophysiology of pain in PD, mainly with the involvement of BG and the reduction of dopamine, the optimization of antiparkinsonian therapy, (e.g., levodopa or dopaminergic agonists) will have beneficial effects and may be the first step in the treatment of PD pain[203]. This hypothesis is supported by clinical observations in which pain tends to occur during off periods[229,235] and that levodopa normalizes the abnormal pain perception in BG[173,236].

The RECOVER study evaluated the effect on motor symptoms of rotigotine, a dopaminergic agonist, versus placebo in a subpopulation of PD patients with nocturnal and early morning problems[237]. The authors subsequently performed an exploratory analysis and found that rotigotine improved pain compared to the placebo[237]. Subsequently, the DOLORES study was performed to evaluate the analgesic effect of rotigotine versus placebo on PD pain[238]. This study confirmed the improvement in PD pain with rotigotine, but the absolute improvement did not reach the statistically significant difference between the two groups and it was not possible to determine which pain subtype improved[238].

A post-hoc analysis of data from studies with safinamide, a MAO-inhibitor, showed a significant reduction in the number of pain treatments[239]. And another post-hoc analysis showed that the benefit of safinamide in the treatment of PD pain seems to be long term, remaining at least for two years[240]. Qureshi et al. published the first systematic review and meta-analysis of PD pain with 24 studies published between January 2014 and February 2018[241]. The finding that safinamide can be an adjuvant drug in the treatment of pain in PD[242]. An open-label study in 14 patients with continuous intestinal infusion of levodopa gel showed improvement in nocturnal dystonic nocturnal pain[243].

As pain in PD can be mediated by neurotransmitters other than dopamine, drugs with other mechanisms of action have been tested. An open-label study evaluated the efficacy of duloxetine, an inhibitor of serotonin and norepinephrine reuptake, in the treatment of pain in PD[244]. Thirteen of the twenty patients who completed the study had subjective improvement of pain but did not change the pain threshold on neurophysiological tests[244]. In the double-blind, randomized controlled trial PANDA, an opioid (n=93), oxycodone in combination with naloxone, versus

placebo (n=109) was tested in the treatment of PD patients who had at least one type of severe pain[245]. This study showed improvement in pain with oxycodone in the first weeks (4, 8, and 12 weeks) but did not show at 16 weeks, which was the main endpoint of the study. The authors suggest that treatment may be effective in less severe pain and that, considering the good safety profile, higher doses may be tested in younger patients with severe pain in future studies[245]. In the treatment of localized pain in PD patients, studies have demonstrated the efficacy of botulinum toxin[246,247]. Currently there is no clear evidence to support the use of specific analgesic medication (e.g., paracetamol, non-steroidal anti-inflammatory drugs) in PD[248].

Most neurologists treat patients with chronic pain, but only a few have received any training in pain treatment in PD patients[116]. To help, practical recommendations from experts have been published in recent years. Based on the pathophysiology, Geroin et al. suggest the use of antiparkinsonian drugs (e.g., levodopa or dopaminergic agonists) and paracetamol or non-steroidal anti-inflammatory drugs in the treatment of nociceptive pain and the use of opioids, levodopa, or gabapentin in the treatment of neuropathic pain[248]. Rana et al. published a review of the literature on pharmacological treatment of pain in PD[249]. They reported that drugs used to treat motor symptoms on PD (levodopa, levodopa/carbidopa/entacapone, bromocriptine, pramipexole, rotigotine and apomorphine) and other drugs (botulinum toxin, oxycodone and duloxetine) have effects on pain reduction in PD[249]. Antonini et al. recommended that fluctuation-related pain may respond to adjustments in dopaminergic therapy; dystonic pain may respond to botulinum toxin injections; and central pain may respond to central pain-modulating medications; therefore, the clinician should ensure that the patients' current dopaminergic therapy is optimized[116].

Non-pharmacological

Studies have shown that DBS (STN or GPi) substantially improves pain in PD, up to 87%, particularly during off periods[250-253]. Dystonia-related pain is the most responsive (almost 100%), followed by central parkinsonian pain (92%), radicular-neuropathic pain (63%) and musculoskeletal pain (61%)[250,254]. Sürücü et al.

conducted a study in which they demonstrated that DBS-STN was more effective in improving pain in PD than the best medical therapy and that this improvement can be estimated with the acute levodopa test[252]. The improvement of pain in PD with DBS-STN has not been correlated with the improvement of motor symptoms, mood, or dopaminergic therapy, but it is associated with a direct effect of DBS in increasing pain thresholds and improving sensory and affective components of pain in PD patients[145,255]. Some authors argue that in PD patients with severe and disabling pain, DBS-STN should be considered the best treatment[252]. The effectiveness of DBS-STN in the treatment of pain in PD appears to be maintained over the long term. In the studies of Oshima et al.[256] and of Pellaprat et al.[255] the improvement continued after 12 months; and in the studies of Kim et al. the improvement continued at 2 years[257] and at 8 years[254]. Pain reduction correlates with improved quality of life after DBS-STN[251]. Other studies have shown the effectiveness of unilateral pallidotomy[258] and spinal cord stimulation in the treatment of pain in PD.[259,260]

Some studies evaluated the effect of exercise on pain in PD patients. In one study, 20 PD patients underwent an exercise program for 12 weeks and showed an improvement in pain of 8%, which was not statistically significant[261]. In another study PD patients (n=90) who underwent 6 months of walking exercises (versus relaxation and flexibility exercises) showed improvement in pain[262]. This effect of exercise may be due to the modulation of dopaminergic and non-dopaminergic inhibitory pathways, the promotion of neuroplasticity, and a relief of the mechanical contribution to pain[263-265]. There is some evidence that pain may improve with acupuncture[266] or with Japanese massage[267]. Some preliminary studies have shown improvement of pain in PD with electromagnetic therapy[268,269]. The role of complementary and alternative medicines in pain management in PD has not yet been established.

One of the main limitations of these studies of the treatment of pain in PD is the classification of pain in PD as a homogeneous entity when it is not[242,270]. Different pain subtypes in PD respond differently to treatments, so careful diagnosis and classification of pain is critical. Therefore, future studies with a better characterization of subtypes of pain in PD are needed.

In the treatment of pain in PD it is also important to consider secondary causes of pain, such as lower limb edema caused by dopaminergic agonists or abdominal pain caused by constipation, and comorbidities should be considered, as pain can be imputed to a non-PD causes including cancer, arthritis or diabetes[116].

In summary, the clinician when approaching a PD patient with pain the clinician should understand which subtype or subtypes of pain the patient presents because the causal mechanism is different and the treatment should be individualized. As an initial strategy, dopaminergic therapy should be optimized in all patients because some pain subtypes respond well to dopaminergic medication. In individualized treatments, for example, there is evidence that patients with central parkinsonian pain or related motor fluctuations may respond well to DBS-STN, or local dystonic pain may respond well to botulinum toxin or central parkinsonian pain may respond to modulatory therapy (e.g., duloxetine or gabapentin). Although there are no studies focusing on the integration of pharmacological and non-pharmacological approaches, it should be considered that, as with pain management in general, a multidisciplinary approach to pain management is also required in PD.

Personal motivation for the thesis “Pain in Parkinson's Disease”

In my daily clinical practice as a neurologist who follows patients with PD, I have noticed the high frequency of non-motor symptoms and the consequent loss of quality of life in these patients. I also found that PD patients, most of the time, do not associate many of these symptoms with PD and they need to be proactively inquired about and investigated.

Empirically, I noticed that pain was one of the most frequent non-motor symptoms. Often, pain was the symptom that bothered them the most and, in some patients, pain seemed to arise before the motor symptoms of PD. In some of these patients, notably in younger patients, the pain was unrelated to musculoskeletal disorders or motor symptoms of PD (e.g., dystonia). It was a pain that was difficult to characterize, which incapacitated them and did not improve with the usual analgesic treatments. For these reasons, I conducted bibliographic research on pain in PD and found that published studies were scarce and, as intuited by my clinical practice, the studies that existed showed that pain, despite being very common, was underdiagnosed and undertreated in PD patients. Therefore, I came up with the idea of conducting a study on pain in PD that would provide good epidemiological data and increase knowledge in this specific area. I prepared and presented a draft of the study on pain in PD to the multidisciplinary group of Movement Disorders of Hospital de Santo António, who were receptive and motivated me to work toward the realization of the project.

For the implementation of the project, I sought to provide myself with better resources and knowledge of clinical research and so I applied and was accepted into the PhD program in Clinical and Health Services Research of Faculty of Medicine - University of Porto. This PhD program with unique characteristics in Portugal allowed me to develop skills to design and implement research work and to produce original research. I also sought supervisors with important knowledge and experience in this area of research who would help me in conducting the research that would culminate in the development of this doctoral thesis.

In summary, the primary personal motivation for conducting this research on the topic of pain in PD arose from my clinical practice as a neurologist who follows PD patients.

CHAPTER II | Aims

Aims

The research work that constitutes this PhD thesis had these main objectives:

1. To determine the prevalence and characteristics of pain and pain subtypes in PD

2. To explore the demographic and clinical predictors of pain in PD. Investigate the relationship between pain, particularly central parkinsonian pain, and demographic and clinical characteristics in PD

3. To investigate the relationship between pain and central parkinsonian pain, and other symptoms in PD, both motor and non-motor

4. To investigate the relationship of central parkinsonian pain and antiparkinsonian treatments

5. To put forward a clinical characterization of the PD subtype Park pain

We hypothesized:

1. Pain is a common non-motor symptom and musculoskeletal pain is the most frequent subtype of pain. Central parkinsonian pain prevalence is around 15%. Pain in PD is intense and causes disability.

2. PD patients with central parkinsonian pain have distinctive demographic and clinical features.

3. PD patients with pain and central parkinsonian pain have more severe motor symptoms. PD patients with central parkinsonian pain have a specific

pattern of non-motor symptoms (e.g., sleep, depression, anxiety, impulse control, smoking habits, and cognitive function).

4. The central parkinsonian pain improves with antiparkinsonian treatment.

5. Park pain subtype is characterized by unique clinical features.

To achieve these objectives, we conducted an observational study in a large cohort of patients with PD.

CHAPTER III | Participants and methods

Participants and methods

To achieve the objectives of this research project, we proposed to conduct a large observational study in PD patients at the Movement Disorders Clinic - Neurology Service, Neurosciences Department of Centro Hospitalar Universitário do Porto (CHUPorto).

Participants

Three hundred and twenty-two consecutive patients with diagnosis of PD according to the United Kingdom Brain Bank criteria were identified[92]. Exposure to neuroleptics, vascular parkinsonism, possible or probable atypical parkinsonian syndromes, and advanced therapies (subcutaneous apomorphine pump, levodopa-carbidopa intestinal gel, or deep brain stimulation) were considered a priori exclusion criteria. Among the 322 possible subjects, only one refused to participate in the study. Of those included (n=321), 6 died (2 patients from respiratory infection, 1 from heart disease, and 3 from unknown cause), 2 were excluded because they developed other debilitating conditions, 13 moved geographically to a region not dependent on our center or could not be reached between inclusion and assessment, and 8 could not be assessed due to logistical problems. In the first study, 292 PD patients participated.

After the clinical evaluation of the 292 PD patients, for the second study, 63 patients were excluded (1 due to misdiagnosis and 62 dues to incomplete data), and 229 patients participated. For the third study, 32 patients were excluded (27 were illiterate (i.e., had less than three years of education)) and 5 were excluded after the assessment (i.e., due to an inability to complete the Dementia Rating Scale-2 (DRS-2)), and 260 participated in the study (Figure 1).

The study was authorized by the Administrative Council of Centro Hospitalar Universitário do Porto, following a favorable opinion from the Ethics Committee and the Department of Education, Training and Research. All patients (or legal representatives) were informed about the nature of the study and gave their consent for participation.

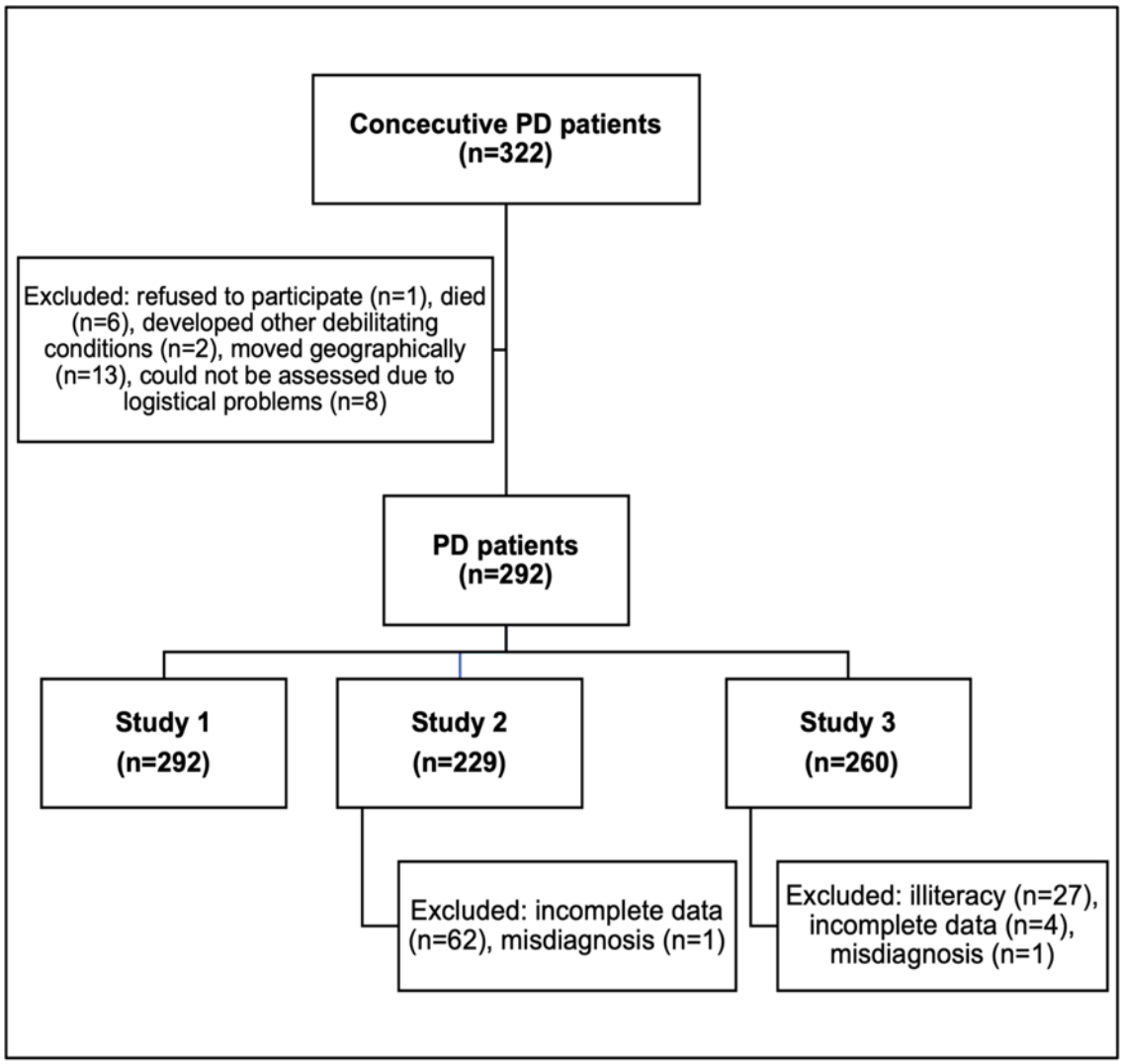

Figure 1. Flowchart of the studies samples

Common procedures

Based on an interview and clinical records, the following data were collected: sex, age, age at PD onset, first motor symptom, age at motor fluctuations onset, age at dyskinesia onset, comorbidities associated with or predisposing to pain (e.g., rheumatic disease, diabetes mellitus, musculoskeletal disorders), and current treatments. Current antiparkinsonian medication was converted to levodopa equivalent dose (LED)[271]. All patients were evaluated in the morning without antiparkinsonian medication for 12 hours (*off* medication condition), using the Unified Parkinson's Disease Rating Scale (UPDRS)[153] and the modified Hoehn & Yahr scale (H&Y)[272]. After the assessment in *off*, patients took their usual first dose

of antiparkinsonian medication and were re-evaluated 1 hour later (*on* medication condition) using the same instruments. Then, the Schwab and England Independence Scale (S&E)[273] was applied. S&E referred to *off* and *on* state conditions.

All patients were then asked whether they had pain in the last month. Those who responded "yes" were asked a series of questions regarding their pain: onset; duration; localization; features (e.g., burning, tingling, formication, stabbing, aching, tension, tightness, or radiating); intensity; frequency; precipitating/relieving factors; temporal and topographical relationship with PD symptoms; and influence of motor complications, motor fluctuations, dyskinesia and dopaminergic medication. In cases with multiple subtypes of pain, pain onset and duration referred to the oldest pain subtype. Based on the patients' description, the neurologist categorized the pain, according to Ford framework[119], as central parkinsonian pain, musculoskeletal pain, radicular/neuropathic pain, dystonia-related pain, and/or akathitic discomfort. Potential causes of pain other than PD were explored (by clinical evaluation and a review of the existing complementary exams on the clinical chart) and were excluded when classifying central parkinsonian pain. The Brief Pain Inventory (BPI) and the Pain Disability Index (PDI) were applied whenever possible (i.e., patient's ability to answer the questions and availability of time to apply the questionnaires)[151].

Patient evaluations were performed by movement disorders' specialists and neuropsychologists experienced in the evaluation of PD patients.

Statistical analysis

Descriptive statistics were used for group characterization and non-parametric tests (i.e., Chi-Square Test, Fisher's Exact, and Mann-Whitney Test) for group comparisons. Logistic regressions were applied to explore predictors of pain and sleep disorders. The threshold for statistical significance was $p<0.05$ for group comparisons and logistic regressions. The statistical analysis was conducted using the Statistical Package for the Social Sciences version 25.0 (SPSS, USA).

For each sub-study, specific methodologies and data analyses were adopted and are described in the respective articles.

CHAPTER IV | Publications

Article I

Unveiling the Relationship Between Central Parkinsonian Pain and Motor Symptoms in Parkinson's Disease

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ORIGINAL ARTICLE

EJP European Journal of Pain WILEY

Unveiling the relationship between central parkinsonian pain and motor symptoms in Parkinson's disease

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Abstract

Background: Pain in Parkinson's disease (PD) is a common and heterogeneous non-motor symptom. Although the characteristics and predictors of pain in general and of central pain in particular are still largely unknown.

Methods: A semi-structured interview, the Brief Pain Inventory and the Pain Disability Index were used to identify and characterize pain in a consecutive series of 292 PD patients. Unified PD Rating Scale-III, Hoehn & Yahr, Schwab and England Independence Scale and Freezing of Gait Questionnaire were applied to assess motor symptoms and functional independence in off and on conditions. Hospital Anxiety and Depression Scale and Questionnaire of Impulsive-Compulsive Control Disorders were used to screen for anxiety, depression and impulse control disorders.

Results: Two hundred and twelve patients (73%) reported pain, which was classified as: musculoskeletal (63%), dystonia-related (27%), central parkinsonian (22%) and/or radicular or neuropathic (9%). Patients with pain had more comorbidities and more severe motor symptoms. Patients with central parkinsonian pain were significantly younger, had earlier disease onset, fewer comorbidities, greater non-axial motor symptom severity in on, more pain-related disability and more relief of pain with antiparkinsonian medication than patients with non-central parkinsonian pain.

Conclusions: PD patients with central parkinsonian pain have some distinctive demographic and clinical features, including lower levodopa responsiveness of motor appendicular/limb symptoms to levodopa, associated with greater responsiveness of pain symptoms to these same medications. These findings suggest the need for a more integrated approach to motor and non-motor symptoms in these patients' clinical care.

Significance: In a consecutive series of 292 patients with PD, almost three quarters of patients with PD reported pain. The study results revealed that pain was related to more severe motor symptoms, anxiety symptoms and comorbidities. Among patients with pain, those with central parkinsonian subtype had distinct demographic and clinical features, including lower levodopa responsiveness for non-axial motor symptoms and greater responsiveness of pain to antiparkinsonian treatment.

1 | INTRODUCTION

Pain is a frequent component of many neurological disorders, including Parkinson's disease (PD) (Borsook, 2012). PD is the second most common neurodegenerative disease (Nussbaum & Ellis, 2003) and has been classically described as a disease with motor symptoms, such as bradykinesia, tremor at rest, rigidity and postural instability (Herzberg, 1990). Although, PD is a complex neurodegenerative disorder that also includes non-motor symptoms, such as dementia, depression, sleep disorders, autonomic dysfunction and sensory symptoms (Langston, 2006).

Pain is a major and disabling non-motor symptom in PD, with a prevalence of up to 85% (Broen, Braaksma, Patijn, & Weber, 2012; Defazio, Gigante, Mancino, & Tinazzi, 2013; Ha & Jankovic, 2012). Pain in PD has been viewed as a manifestation of the disease and/or a consequence of PD motor symptoms (Defazio et al., 2008). The pathophysiology of pain in PD patients remains undefined, but clinical, neurophysiological, functional imaging data in PD and in the general population have implicated the basal ganglia (BG) in pain processing (Brefel-Courbon et al., 2005; Schestatsky et al., 2007). Further evidence of this involvement is the reduction of pain when PD patients take levodopa or dopamine agonists (Brefel-Courbon et al., 2005). Some patients with pain may experience dopamine dysregulation syndrome (DDS), which is characterized by self-medication and an addiction to dopaminergic drugs in excess to control motor symptoms and the discomfort related to non-motor symptoms such as pain (Kummer, Maia, Salgado, Cardoso, & Teixeira, 2006; Sierra et al., 2015). The possibility of different non-motor clinical subtypes of PD has been discussed and a Park pain phenotype has been proposed (Sauerbier, Jenner, Todorova, & Chaudhuri, 2016).

The relationship between pain and motor symptoms and motor complications is controversial. Some studies have found associations with severity of disease and motor complications (Negre-Pages, Regragui, Bouhassira, Grandjean, & Rascol, 2008; Tinazzi et al., 2006), whereas others have reported non-significant findings (Beiske, Loge, Ronningen, & Svensson, 2009; Defazio et al., 2008; Gierthmuhlen et al., 2010). These inconsistent findings can be at least partly explained by the non-differentiation between subtypes of pain (Beiske et al., 2009).

Central pain is one of five subtypes of pain in PD identified by Ford (Ford, 2010) and it is assumed to be the only subtype of pain that is a direct consequence of the disease itself, resulting from abnormal painful information processing, and not the result of dystonia, rigidity or a musculoskeletal cause (Canavero, 2009; Ford, 2010; Zambito-Marsala et al., 2017). Central pain is PD is often described as a diffuse burning sensation. It is not related to a lesion in the peripheral nervous system and does not fulfil the current criteria for central neuropathic pain (Treede et al., 2008). Central parkinsonian pain has been suggested as a more accurate term (Cury et al., 2016). The association between central parkinsonian pain and motor symptoms is still largely unknown and the relationship between central parkinsonian pain perception and treatment for PD is still a matter of debate. Some studies have provided evidence of improvement of central parkinsonian pain with antiparkinsonian drugs (Brefel-Courbon et al., 2005; Schestatsky et al., 2007) or deep brain stimulation of the subthalamic nuclei (Cury et al., 2014; Marques et al., 2013). Although, other studies did not find significant effects. (Djaldetti et al., 2004; Gierthmuhlen et al., 2010) These inconsistent reports could be, at least, partly explained by the small samples and the methodological differences.

The aims of the present study were: (1) to examine the prevalence of pain and pain subtypes in PD, (2) to investigate the relationship between central parkinsonian pain and demographic and clinical characteristics and (3) to study the relationship between antiparkinsonian treatment and central parkinsonian pain. We hypothesize that patients with central parkinsonian pain have distinctive demographic and clinical features and that central parkinsonian pain is ameliorated with antiparkinsonian drugs.

2 | MATERIALS AND METHODS

2.1 | Participants

A cross-sectional study was carried out in the Movement Disorders Clinic of Centro Hospitalar do Porto. Three hundred and twenty two consecutive patients with diagnosis of PD according to the United Kingdom Brain Bank criteria were identified (Hughes, Daniel, Kilford, & Lees, 1992). Exposure to neuroleptics, vascular parkinsonism, possible or probable atypical parkinsonian syndromes and advanced therapies (subcutaneous apomorphine pump, levodopa-carbidopa intestinal gel or deep brain stimulation) were considered a priori exclusion criteria. From the 322 possible subjects, only one refused to participate in the study. From those included (n = 321), 6 died (2 patients from respiratory infection, 1 from heart disease and 3 from unknown cause), 2 were excluded because they developed other debilitating conditions, 13 moved geographically to a region not dependent from our centre or could not be reached between inclusion and assessment and 8 could not be assessed due to logistic problems. A total of 292 PD patients participated in the study.

All the patients (or legal representatives) were informed about the nature of the study and gave their consent for participation. The ethics committee of the Centro Hospitalar do Porto approved the study.

2.2 | Procedures

Based on an interview and on clinical records, the following data were collected: sex, age, age at PD onset, first motor symptom, age at motor fluctuations and dyskinesia onset, comorbidities associated with or predisposing to pain (e.g., rheumatic disease, diabetes mellitus, musculoskeletal disorders) and current treatments. Current antiparkinsonian medication was converted to levodopa equivalent dose (LED) (Tomlinson et al., 2010).

A movement disorder specialist performed a neurological examination to all participants. Thirty patients (10%) were evaluated at home due to the severity of their motor symptoms. PD patients were evaluated in the morning without antiparkinsonian medication for 12 hr (off medication condition), using the Unified PD Rating Scale (UPDRS) (Fahn et al., 1987) and the modified Hoehn & Yahr scale (H&Y) (Hoehn & Yahr, 1967). After the assessment in off, patients took their usual first dose of antiparkinsonian medication and were re-evaluated one hour later (on medication condition), using the same instruments. Then, the Schwab and England Independence Scale (S&E) (Schwab & England, 1969), the freezing of gait questionnaire (FOG-Q) (Giladi et al., 2000) were applied. S&E referred to off and on state conditions. Based on UPDRS-III off and on, an axial index (sum of items 18, 27, 28, 29 and 30) and a non-axial index [sum of items 20 (except face, lips and chin tremor), 21, 22 (except neck rigidity), 23, 24, 25 and 26] were calculated (Bejjani et al., 2000; Mendes et al., 2016).

Each PD patient was classified as having tremor-dominant, postural instability and gait difficulty (PIGD) or indeterminate phenotype according to the dominance of the motor symptoms in the UPDRS II and III subscales (Jankovic et al., 1990).

All patients were then asked whether they had pain in the last month. Those who responded "yes" to the previous question were asked a series of questions regarding their pain: onset; duration; localization; features (including burning, tingling, formication, stabbing, aching, tension, tightness or radiating); intensity; frequency; precipitating/relieving factors; temporal and topographical relationship with PD symptoms; and influence of motor complications, motor fluctuations, dyskinesia and dopaminergic medication. In case of multiple subtypes of pain, pain onset and duration referred to the oldest subtype of pain. Based on the patients' description, the neurologist categorized the pain, according to Ford framework (Ford, 2010), as central parkinsonian pain or non-central parkinsonian pain (i.e., musculoskeletal pain, radicular/neuropathic pain, dystonia-related pain and akathitic discomfort). Central parkinsonian pain was defined, according to Ford criteria (Ford, 2010), as burning, tingling, formication, or "neuropathic" sensations, often relentless and bizarre in quality, not confined to root or nerve territory, and not explained by rigidity, dystonia, musculoskeletal or internal lesion. Central parkinsonian pain may have an autonomic character, with visceral sensations or dyspnoea, and may vary in parallel with the medication cycle as a non-motor fluctuation. Potential causes of pain other than PD were explored (by clinical evaluation and review of the existing complementary exams on the clinical chart) and excluded when classifying central parkinsonian pain. The Brief Pain Inventory (BPI) and the Pain Disability Index (PDI) were applied whenever it was possible (i.e., patient's ability to answer the questions and availability of time to apply the questionnaires) (Azevedo, Dias, Agualusa, & Lemos, 2007). The Hospital Anxiety and Depression Scale (HADS) was applied to measure anxiety and depression; a cut-off score of ≥8 was used for each subscale (Pais-Ribeiro et al., 2007). The Questionnaire of Impulsive Compulsive Disorders in PD short current was applied to identify DDS (Weintraub et al., 2009).

2.3 | Statistical analysis

Descriptive statistics were used for group characterization and non-parametric tests (i.e., Chi-Square Test, Fisher's Exact and Mann-Whitney Test) for group comparisons. Pearson's correlation was applied to explore associations between variables. Simple and multiple logistic regression models were applied to explore associations between pain variables and a series of independent variables.

The threshold for statistical significance was $p < 0.05$ for group comparisons and for logistic regressions. To avoid type I errors due to multiple correlations, a threshold of $p < 0.001$ was used for Pearson's correlations. The statistical analysis was conducted using the Statistical Package for the Social Sciences version 25.0 (SPSS, USA).

3 | RESULTS

3.1 | Characteristics of the sample

Of the 292 PD patients examined, 148 (51%) were men, their mean age was 69.6 ± 11.0 years, mean age at disease onset was 60.3 ± 11.8 years, and mean duration of the disease was 9.3 ± 6.3 years. Two hundred and eighty-eight (99%) patients were taking levodopa and/or dopamine agonist. One hundred and thirteen (39%) were taking dopamine agonist (108 ropinirole, 2 pramipexole, and 3 piribedil). The mean LED was 903.5 ± 519.2 mg/day. Their mean scores in motor scales were: 34.3 ± 12.2 in UPDRS-III off and 24.1 ± 10.9 in on; 2.8 ± 0.9 in Hoehn and Yahr score in off and 2.5 ± 0.7 in on; and 7.5 ± 6.5 in FOG-Q. The mean scores in the functional independence scale S&E were: 72.0 ± 19.5 in off and 83.6 ± 15.2 in on. A total of 179 (61%) PD patients had motor fluctuations

and 106 (36%) had dyskinesia. The frequencies of anxiety and depression were, respectively, 124 (46%) and 135 (50%).

3.2 | Prevalence and characterization of the pain

At the time of the assessment, 212 patients (73%) reported pain, with a median duration of 5 years (interquartile interval: 2–12; Table 1). Sixty-eight (32%) PD patients reported that the pain developed before motor symptoms of PD and 105 (50%) referred relief of pain with antiparkinsonian therapy. Of those with pain, 133 (63%) had musculoskeletal pain, 57 (27%) had dystonia-related pain, 46 (22%) had central parkinsonian pain, and 19 (9%) had radicular/neuropathic pain. No one reported akathitic discomfort. One hundred and sixty five patients (78%) reported only one subtype of pain and 47 (22%) reported two or more subtypes of pain. One hundred and fifty nine patients (82%) have had pain for more than a year. Pain was reported to be constant in 133 (63%), intermittent in 60 (28%) and sporadic in 18 (9%) patients. Thirty-five patients (16%) rated the pain as severe, 125 (60%) as moderate, and 50 (24%) as mild. The median BPI severity and interference scores were, respectively, 13 and 27, and the median PDI was 23.

3.3 | Comparison between PD patients with and without pain

Table 1 shows the demographic and clinical features of patients with and without pain. The severity of the motor symptoms was greater (as measured by the H&Y in off and on, the axial index in off and the FOG-Q), the frequency of motor fluctuations was higher, the duration of the off state was longer, and the LED was higher ($p < 0.05$) among PD patients with pain. Patients with pain also had lower functional independence (as measured by S&E in off and on states), more comorbidities (in particular osteoarticular pathology), and more anxiety (as measured by HADS ≥ 8) than patients without pain. The motor phenotype was different between patients with and without pain ($p = 0.012$). A simple logistic regression revealed that the odds of having pain were lower among patients with a predominant tremor phenotype (odds = 0.430, 95% CI: 0.235–0.788; $p = 0.006$) than with an akinetic rigid or a mixed phenotype. No significant differences ($p > 0.05$) were found between patients with and without pain regarding: sex, age, age at disease onset, disease duration, axial index on, non-axial index in off and on, dyskinesia, dopamine agonists, presence of DDS or depression.

While considering sex, age at disease onset, and comorbidities as covariates, higher H&Y in off and on, lower S&E in on, higher FOG-Q, non-tremor motor phenotypes and motor fluctuations remained statistically associated ($p < 0.05$) with pain (Table 2).

3.4 | Pain severity, interference and disability

Among patients with pain, BPI severity score was significantly ($p < 0.001$) but weakly related with UPDRS-III in on ($r = 0.261$) and off ($r = 0.283$), and non-axial symptoms in on ($r = 0.262$) and off ($r = 0.290$). PDI score was related ($p < 0.001$) with UPDRS-III in on ($r = 0.307$) and off ($r = 0.304$), S&Y in off ($r = -0.301$) and axial symptoms in on ($r = 0.271$) and off ($r = 0.294$). Higher BPI severity and interference scores and PDI scores were significantly related to female sex and with the presence of osteoarticular disorders, non-tremor motor phenotype, anxiety and depression. No significant associations ($p > 0.001$ for bivariate correlations and $p > 0.05$ for group comparisons) were found with age, age at disease onset, disease duration, diabetes, FOG, motor fluctuations, dyskinesia, agonist medication and LED.

3.5 | Comparison between central parkinsonian pain and non-central parkinsonian pain

Among PD patients with only one subtype of pain ($n = 165$), 34 (21%) had central parkinsonian pain and 131 (79%) had non-central parkinsonian pain (56% musculoskeletal pain, 13% radicular/neuropathic pain and 10% dystonia-related pain). Table 1 shows that patients with central parkinsonian pain were younger, had earlier disease onset, fewer comorbidities, lower frequency of pain onset prior to motor symptoms, more pain-related disability as measured by PDI, but greater relief of pain with antiparkinsonian medication ($p < 0.05$) than those with non-central parkinsonian pain. Patients with central parkinsonian pain also had more severe non-axial symptoms in on, but lower stage of the disease as measured by H&Y in on ($p < 0.05$). No significant differences were found regarding sex, disease duration, UPDRS-III in on, S&E in off and on, FOG-Q, motor phenotype, axial index in off and on, motor fluctuations, dyskinesia, dopamine agonist, LED, presence of DDS, duration of pain, BPI severity and interference scores or anxiety and depression ($p > 0.05$).

While considering age (or age at disease onset) and comorbidities as covariates, lower H&Y in on, higher non-axial index in on, more severe PDI and greater relief of pain with antiparkinsonian medication remained significantly associated ($p < 0.05$) with central parkinsonian pain (Table 2).

Patients who reported relief of pain with antiparkinsonian medication had lower H&Y in on ($p = 0.007$), but not in off ($p = 0.883$) in comparison to those who did not experience relief. Also, there was a tendency for more motor fluctuations in the subgroup of patients with relief of pain with

TABLE 1 Demographic, clinical and therapeutic characteristics of PD patients with ($n = 212$) and without pain ($n = 80$) and of PD patients with central parkinsonian pain ($n = 34$) and with non-central parkinsonian pain ($n = 165$)

	With pain ($n = 212$)	Without pain ($n = 80$)	*p*	Central parkinsonian pain ($n = 34$)	Non-central parkinsonian pain ($n = 131$)	*p*
Sex—men	100 (47%)	48 (60%)	0.050	15 (44%)	68 (52%)	0.418
Age	71 (63–77)	73 (65–79)	0.144	68 (57–73)	72 (65–78)	0.009
Age at disease onset (years)	61(53–68)	63 (56–70)	0.062	58 (50–66)	63 (54–70)	0.030
PD disease duration (years)	8 (5–12)	6 (4–12)	0.088	6 (4–10)	8 (5–13)	0.086
Comorbidities (Diabetes or Osteoarticular)	94 (44%)	21 (26%)	0.005	8 (24%)	67 (51%)	0.004
Diabetes	30 (14%)	12 (15%)	0.854	2 (6%)	21 (16%)	0.169
Osteoarticular	75 (35%)	9 (11%)	<0.001	8 (24%)	53 (41%)	0.068
UPDRS III off	33 (26–43)	31 (24–39)	0.089	36 (28–44)	33 (26–43)	0.283
UPDRS III on	23 (16–30)	22 (16–28)	0.247	27 (20–31)	23 (17–30)	0.073
H&Y off	3 (2–3)	2 (2–3)	0.002	2.5 (2–3)	3 (2–3)	0.123
H&Y on	2.5 (2–3)	2 (2–2.5)	0.033	2 (2–2.5)	2.5 (2–3)	0.005
S&E off	80 (60–90)	80 (70–90)	0.020	75 (70–80)	80 (60–90)	0.916
S&E on	90 (80–90)	90 (80–100)	0.030	90 (80–90)	90 (80–90)	0.212
FOG-Q	6 (2–13)	4 (1–10)	0.010	8 (2–12)	5 (2–13)	0.990
Motor phenotype						
Akinetic rigid	153 (72%)	51 (64%)	0.012	22 (65%)	88 (67%)	0.760
Tremor	33 (16%)	24 (30%)		8 (24%)	24 (18%)	
Mixed	26 (12%)	5 (6%)		4 (12%)	19 (15%)	
Axial Index off	6 (4–9)	5 (3–8)	0.030	6 (4–8)	6 (4–9)	0.899
Axial Index on	4 (3–7)	4 (2–7)	0.109	4 (2–6)	4 (3–8)	0.510
Non-Axial Index off	22 (16–27)	21 (15–25)	0.156	26 (16–30)	22 (17–26)	0.102
Non-Axial Index on	14 (10–18)	14 (9–17)	0.330	17 (11–22)	13 (10–18)	0.021
Motor fluctuations	141 (67%)	38 (48%)	0.003	21 (62%)	81 (62%)	0.994
Off state duration (item 39 from UPDRS IV)	1 (0–2)	0 (0–1)	0.006	1 (0–1)	1 (0–2)	0.184
Dyskinesia	81 (38%)	25 (31%)	0.270	9 (27%)	48 (37%)	0.266

(Continues)

TABLE 1 (Continued)

	With pain (n = 212)	Without pain (n = 80)	p	Central parkinsonian pain (n = 34)	Non-central parkinsonian pain (n = 131)	p
Dyskinesia duration (years)	3 (2–9)	4 (1–10)	0.840	2 (1–5)	4 (1–8)	0.197
Dopamine agonists	86 (41%)	27 (34%)	0.286	16 (47%)	47 (36%)	0.232
LED (mg/day)	875 (560–1,219)	705 (400–1,063)	0.023	830 (490–1,133)	800 (500–1,180)	0.720
Pain duration (years)	5 (2–12)	–		5 (1–9)	6 (2–15)	0.069
Onset of pain before motor symptoms	63 (33%)	–		6 (19%)	48 (41%)	0.022
BPI—severity	13 (9–17)	–		14 (9–18)	12 (8–16)	0.173
BPI—interference	27 (16–38)	–		29 (21–40)	26 (12–38)	0.165
PDI	23 (12–38)			32 (20–45)	18 (10–35)	0.006
Relief of pain with antiparkinsonian therapy	105 (50%)	–		33 (97%)	37 (29%)	<0.001
HADS—Anxiety ≥ 8	97 (50%)	27 (36%)	0.042	18 (56%)	52 (44%)	0.206
HADS—Depression ≥ 8	102 (52%)	33 (44%)	0.221	15 (47%)	63 (53%)	0.542
DDS	4 (2%)	1 (1%)	>0.999	0 (0%)	4 (3%)	0.582

Note: UPDRS-III on, H&Y on, and S&E on were not applied to non-treated patients (i.e., 1 with central parkinsonian pain, 1 with non-central parkinsonian pain, and 1 without pain). Eighteen patients (i.e., 2 with central parkinsonian pain, 13 with non-central parkinsonian pain, and 3 with multiple pain subtypes) could not recall the onset of pain. BPI and PDI total scores were not calculated in 37 patients (i.e., 3 with central parkinsonian pain, 26 with non-central parkinsonian pain, and 8 with multiple pain subtypes) and 48 patients (i.e., 3 with central parkinsonian pain, 29 with non-central parkinsonian pain, and 16 with multiple pain subtypes) respectively due to incomplete dataset. HADS anxiety and depression scores were also not calculated in 22 patients (i.e., 2 with central parkinsonian pain, 12 with non-central parkinsonian pain, 3 with multiple pain subtypes, and 5 without pain). The missing data correspond to not-applicable (i.e., the patient is unable to answer one or more questions) or logistical limitations (i.e., time constraints). Data are presented as frequencies (%) and as medians (25th–75th percentiles). Chi-square test (or Fisher's exact when appropriate) and Mann-Whitney test were used for group comparisons.

TABLE 2 Associations between pain or subtype of pain and a series of clinical variables

Dependent variable	Independent variable of interest		Multiple logistic regression	
No pain (0) versus pain (1)		Adjusted Odds a	95% CI	*p*
	H&Y off	1.499	1.06–2.11	0.021
	H&Y on	1.670	1.04–2.68	0.034
	S&E off	0.988	0.97–1.00	0.102
	S&E on	0.979	0.96–0.99	0.045
	FOG-Q	1.053	1.01–1.10	0.023
	Tremor phenotype	0.496	0.27–0.93	0.028
	Axial index off	1.068	0.99–1.14	0.063
	Axial index on	1.085	0.99–1.18	0.052
	Motor fluctuations	1.984	1.13–3.47	0.017
	Off state duration (item 39 from UPDRS IV)	1.377	0.99–1.90	0.051
	LED	1.000	1.00–1.00	0.122
	HADS—Anxiety ≥ 8	1.323	0.73–2.39	0.354
Non-central parkinsonian pain (0) versus central parkinsonian pain (1)		Adjusted Odds b	95% CI	*p*
	H&Y on	0.396	0.15–1.06	0.064
	Non-Axial index on	1.088	1.02–1.16	0.006
	PDI	1.047	1.02–1.08	0.002
	Relief of pain with antiparkinsonian therapy	78.792	10.14–612.33	<0.001
		Adjusted Odds c	95% CI	*p*
	H&Y on	0.337	0.13–0.85	0.022
	Non-axial index on	1.067	1.01–1.13	0.026
	PDI	1.044	1.02–1.07	0.003
	Relief of pain with antiparkinsonian therapy	92.658	11.73–731.67	<0.001

Note: Multiple logistic regression analyses were used to further explore the associations identified in Table 1 between pain or subtype of pain and a series of clinical variables. Each independent variable of interest was analysed separately. The covariates applied for each analysis were: (a) sex, age at disease onset, and comorbidities; (b) age and comorbidities; and (c) age at disease onset and comorbidities.

antiparkinsonian medication ($p = 0.056$). A multiple logistic regression analysis revealed that relief of pain with antiparkinsonian medication remained significantly associated with central parkinsonian pain (adjusted odds = 80.30; $p < 0.001$) and presence of motor fluctuations (adjusted odds = 3.29; $p = 0.009$), but not with H&Y in on (adjusted odds = 0.59; $p = 0.11$), when these were considered as covariates.

4 | DISCUSSION

In a consecutive series of 292 PD patients, the prevalence rate of pain was 73%. This prevalence of pain is consistent with other cohorts of PD (Broen et al., 2012; Defazio et al., 2013; Ha & Jankovic, 2012). Although, it is higher than the general Portuguese population of the same age range, which is 36.7%

(Azevedo, Costa-Pereira, Mendonca, Dias, & Castro-Lopes, 2012). The majority of patients (63%) reported daily pain and most of them (83%) rated it as moderate or severe. These data confirm that pain is a major and a disturbing non-motor symptom in PD patients.

The presence of pain was related to more severe motor symptoms, as measured by H&Y (off and on), FOG-Q, axial index (off), presence of motor fluctuations and longer off state duration. The tremor phenotype was also less frequent among patients with pain. These findings confirm previous reports of significant associations between pain and more severe motor manifestations of PD (Negre-Pages et al., 2008; Tinazzi et al., 2006). Although, other series have failed to find significant associations (Beiske et al., 2009; Defazio et al., 2008; Gierthmuhlen et al., 2010) and in our own cohort, the UPDRS-III score did not significantly differentiate between patients with and without pain. These inconsistent results suggest that the association between pain and motor symptoms may depend in part on the clinical scales used to assess motor symptoms.

Among patients with only one subtype of pain ($n = 165$), it was classified as central parkinsonian in 34 patients (21%) and non-central parkinsonian in 131 patients (79%). Central parkinsonian pain is defined by its clinical features, is believed to be unrelated to a disturbance in motor function, and is presumed to be a direct consequence of PD. The frequency of central parkinsonian pain is somewhat higher than in other studies, which range between 4% and 16% (Beiske et al., 2009; Broen et al., 2012; Defazio et al., 2013; Ha & Jankovic, 2012). This variability could be related to differences in sample size, patient selection procedures, and reliability of the classification. For instance, the paraesthetic sensations of coolness, numbness or tingling may be mistakenly attributed to a central pain syndrome, when further evaluation could have revealed a compressive root or nerve lesion (Ford, 2010). Newer classifications (Chaudhuri et al., 2015; Mylius et al., 2015; Perez-Lloret et al., 2016) may improve the characterization of pain in PD.

Patients with central parkinsonian pain were younger at the time of the assessment and at disease onset, but had more severe non-axial symptoms in on than patients with non-central parkinsonian pain. The association between central parkinsonian pain and earlier onset of PD is consistent with Negre-Pages and colleagues (Negre-Pages et al., 2008) report that patients with PD-related pain had earlier PD onset.

Patients with central parkinsonian pain appear to have more non-axial levodopa-resistant symptoms than patients with non-central parkinsonian pain, despite having similar or even less severe axial symptoms. Future studies ought to further explore the association between central parkinsonian pain and limb symptoms of PD.

In our cohort, as expected osteoarticular disorders were more common in PD patients with pain. However, medical comorbidities, including osteoarticular disorders, were less frequent among patients with central parkinsonian pain than in patients with non-central parkinsonian pain. These results provide support to the notion that central parkinsonian pain is a manifestation of PD (Ford, 2010).

Patients with central parkinsonian pain had more pain-related disability than patients with non-central parkinsonian pain. Although almost all patients (97%) with central parkinsonian pain reported relief of pain with dopaminergic therapy, whereas only 37% of patients with non-central parkinsonian pain experienced improvement with anti-parkinsonian medication. This greater responsiveness to dopaminergic treatment was independent of motor fluctuations. These results provide support to the notion that abnormal sensory detection in PD patients can be improved with dopamine therapy, especially in patients with central parkinsonian pain (Pont-Sunyer et al., 2015; Schestatsky et al., 2007). Deep brain stimulation studies have reported significant relief effect on pain symptoms (Ciampi de Andrade et al., 2012; Cury et al., 2014; Kim et al., 2008), including central pain (Kim et al., 2008). Although, the relationship between sensory/pain changes and improvement of motor symptoms with deep brain stimulation is unclear (Ciampi de Andrade et al., 2012; Cury et al., 2014). This set of findings suggests a complex relationship between pain, motor symptoms and antiparkinsonian treatment, either medication or surgical.

Neurophysiological studies have documented abnormal processing of pain stimuli at central rather than peripheral level in PD (Gerdelat-Mas et al., 2007; Mylius et al., 2009; Zambito-Marsala et al., 2017). The increased subjective pain sensitivity and increased spinal nociception, which appears to be reversible by dopaminergic treatment, suggests the involvement of the dopaminergic system in central nociception and points to the possibility of a reduced descending pain inhibition in PD. It is still unclear whether dopamine has a real antinociceptive effect or only a pain modulation effect (Cury et al., 2016). The present data point to the need for adjustments in dopaminergic therapy when pain is an important and debilitating symptom irrespective of the motor state, in particular for patients with central parkinsonian pain.

In our cohort of PD, as expected, the presence of pain was significantly related with anxiety (Rana, Qureshi, Kachhvi, Rana, & Chou, 2016). However, the frequency of depression was not statistically higher among patients with pain. Also, anxiety and depression symptoms were not significantly different between patients with central versus non-central parkinsonian pain. These negative findings suggest that the association between pain and depression is weaker and even more complex in PD than in other non-PD populations (Velly & Mohit, 2018), partly because either can be a non-motor manifestation of the disease.

One-third of all PD patients with pain referred the development of this symptom prior to the onset of motor

manifestations of PD. This prevalence is somewhat similar to the one reported by another study (Defazio et al., 2008). Non-central parkinsonian pain started 1 to 48 years prior to PD onset. Among patients with central parkinsonian pain, 19% reported having this subtype of pain 1 to 12 years prior to PD motor symptoms, which could correspond to the prodromal stage of PD (Pont-Sunyer et al., 2015). The noradrenergic neurons from the reticular formation and coeruleus/subcoeruleus complex, which innervate the dorsal horn of the spinal cord where they inhibit the ascending nociceptive pathways and control the ascending somatic or visceral sensations, are likely involved in the pathophysiology of pain at the premotor stage of the disease (Hawkes, Del Tredici, & Braak, 2010). These neurons may suffer neurodegeneration prior to those in the substantia nigra that cause the motor symptoms (Braak et al., 2003).

This is single centre observational study of a cohort of patients with PD. The consecutive nature of the recruitment, the extremely high acceptance rate and the large sample size decreased potential selection biases in our study. Although a hospital-based sample may not be perfectly representative of the whole population of PD, our Movement Disorders Outpatient Clinic, as part of the National Health Service with universal coverage, receives PD patients in all stages of the disease. Moreover, in this study, to have a representative sample of the whole population and to avoid losses as much as possible, patients with severe motor symptoms, rendering difficult an evaluation at the hospital, were evaluated at home.

An important strength of this study is the diagnosis of PD and the clinical evaluation by movement disorders specialists, although we acknowledge that in a cross-sectional assessment of patients with PD there is the possibility of misdiagnosis in the initial phases of the disease, namely atypical parkinsonian syndromes.

The exclusion of patients with more than one pain subtypes reduces the potential confounding effects of one type of pain over another. Although the exploration of differences between central and non-central parkinsonian pain among patients with only one type of pain limits the clinical representativeness of the sample. The heterogeneity of the non-central parkinsonian pain group was not addressed in this study, even although some pain subtypes included in the non-central parkinsonian pain group may be related (directly or indirectly) to PD. For instance, radicular/neuropathic pain shares common features with central pain. Although, central parkinsonian pain is not related to a lesion, which would be required to fulfil the current criteria for central neuropathic pain (Jensen et al., 2011; Treede et al., 2008). Nonetheless, the non-application of specific measures of neuropathic pain is a shortcoming of the study.

In summary, the results from our cohort confirmed that pain is a common non-motor symptom in PD and that the presence of pain is associated with more severe motor manifestations of PD. The association between pain and mood appears to be weaker and even more complex in PD than in other non-PD populations. Pain with central features was related to younger age, earlier disease onset, fewer comorbidities, more pain-related disability and greater relief of pain with antiparkinsonian medication. This set of demographic and clinical associations suggests the need for an integrated approach to motor and non-motor symptoms in the clinical care of PD patients with central parkinsonian pain. Future clinical, neurophysiological and neuroimaging studies of sensory symptoms ought to explore central parkinsonian pain as a manifestation of PD and the improvement of central parkinsonian pain should be considered as a treatment outcome in PD.

CONFLICTS OF INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

Authors NVC, SC, AM, AG, ALF and JCL were involved in the project conception. Authors NVC, SC, AM and AG organized the project. Authors NVC, SC, AM, AG, IM, JF and JD were involved in project execution. Author SC designed and executed the statistical analysis. Author NVC drafted the manuscript. All authors reviewed the manuscript.

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Article II

Sleep disturbances in Parkinson's disease are associated with central parkinsonian pain

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ORIGINAL RESEARCH

Sleep disturbances in Parkinson's disease are associated with central parkinsonian pain

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Introduction: Sleep disturbances and pain are common non-motor symptoms in Parkinson's disease (PD). This study aimed to explore the association between these two symptoms in a cohort of patients with PD.

Materials and methods: The Parkinson's Disease Sleep Scale (PDSS-2) was used to identify sleep disturbances in a series of 229 PD patients. The identification and characterization of pain was performed by a semi-structured interview and by the application of the Ford classification and the Brief Pain Inventory (BPI). The Unified Parkinson's Disease Rating Scale-III, Hoehn & Yahr (H&Y), and Schwab and England Independence Scale were used to assess motor symptoms and functional independence in off and on conditions. The Hospital Anxiety and Depression Scale (HADS) and SF-36 were applied to screen for anxiety and depression and to evaluate the quality of life. Non-parametric tests were used for group comparisons and logistic regressions were applied to explore predictors of sleep disturbances.

Results: Seventy-five (33%) patients had clinically relevant sleep disturbances (PDSS-2≥18) and 162 patients (71%) reported pain. Of those with pain, 38 (24%) had central parkinsonian pain. PD patients with sleep disturbances experienced more pain and had more severe motor symptoms, lower functional independence, more anxiety and depression symptoms, and worst quality of life. Among patients with pain, central parkinsonian pain was the subtype of pain with the highest odds of sleep disturbances, even when taking into account motor symptoms (H&Y off), motor fluctuations, intensity of pain (BPI), and symptoms of anxiety and depression (HADS).

Conclusions: The association between pain and sleep disturbances in PD appears to be dependent on subtype of pain. The close relationship between central parkinsonian pain and sleep disturbances in PD raises the possibility of common pathophysiological mechanisms. A better understanding of the relationship between sleep disturbances and central parkinsonian pain may contribute to the development of new care strategies in PD patients.

Keywords: Parkinson's disease, sleep disturbances, central parkinsonian pain

Introduction

Parkinson's disease (PD) has been classically described as a disease with motor symptoms, such as bradykinesia, tremor at rest, rigidity, and postural instability.[1] Though PD is a complex disorder that also includes non-motor symptoms, such as dementia, depression, sleep disorders, autonomic dysfunction, and sensory symptoms.[2] The co-occurrence of certain non-motor symptoms has raised the hypothesis of clinical non-motor subtypes with specific pathophysiological patterns.[3]

Sleep disturbances are a common disabling non-motor symptom in PD, its prevalence varies greatly from 40% to 90% in these patients, and may interfere

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with patients' quality of life.[4] The association between poor sleep quality in PD and symptoms of depression and anxiety has been well established.[5] There is also evidence that common sleep problems, such as sleep-onset insomnia and sleep-maintenance insomnia, may be associated with motor symptoms (eg, nocturnal akinesia) and other non-motor symptoms (eg nocturia, hallucinations).[6,7]

Pain is also a major and disabling non-motor symptom in PD, with a prevalence of up to 85%.[8] Pain is one of the most bothersome non-motor symptoms and is known to be associated with lower quality of life[9] and more severe non-motor symptoms.[10]

In general population, sleep disturbances and pain are frequent co-morbidities. There is evidence from experimental and longitudinal studies that pain and sleep interact in a bidirectional manner and negatively affect each other.[11] In PD, studies have shown that sleep disturbances are a risk factor for pain and vice versa.[10,12–16]

Pain in PD can be classified according to its clinical features in five subtypes.[17] One of the subtypes is central parkinsonian pain, which is believed to be the only subtype of pain that is a direct consequence of the disease itself, resulting from abnormal painful information processing, and not the result of dystonia, rigidity, or a musculoskeletal cause, and is considered a neuropathic pain.[17–20] The association between this subtype of pain with sleep disturbances has yet to be investigated.

The general aims of this study were to identify in a cohort of PD predictors of sleep disturbances and to explore the relationship between sleep disturbances and pain, according to pain features.

Materials and methods

Participants

A cross-sectional study of PD patients (diagnosis according to the United Kingdom Brain Bank criteria)[21] was carried out in the Movement Disorders Clinic of Centro Hospitalar Universitário do Porto. Exposition to drug-induced parkinsonism, vascular parkinsonism, possible or probable atypical parkinsonian syndromes, and advanced therapies (subcutaneous apomorphine pump, levodopa-carbidopa intestinal gel, or deep brain stimulation) were considered a priori exclusion criteria. From a consecutive series of 322 possible subjects (Figure 1), 229 participated in the study. One patient refused to participate in the study. Twenty-six were excluded before assessment (ie, seven died, two developed other debilitating conditions, thirteen moved geographically to a region not dependent from our center or could not be reached between inclusion and assessment, and four could not be assessed due to logistic problems) and 66 were excluded after the assessment (ie, one due to misdiagnosis and 65 due to incomplete data set).

All the patients (or legal representatives) were informed about the nature of the study and gave written informed consent, in compliance with the Declaration of Helsinki. The ethics committee of Centro Hospitalar e Universitário do Porto approved the study.

Procedures

Based on an interview and clinical records, the following data were collected: sex, age, age at PD onset, first motor symptom, and current treatments. Current antiparkinsonian

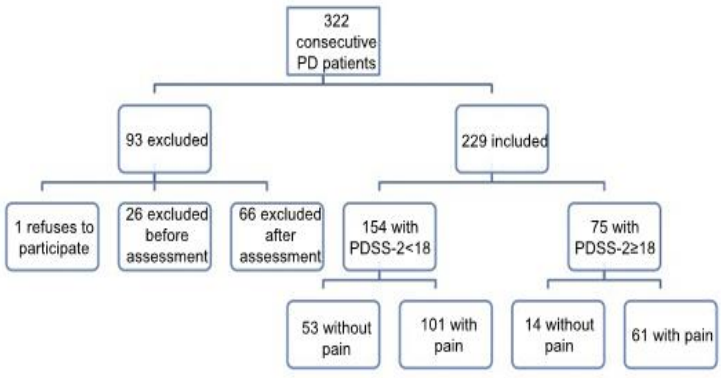

Figure 1 Flowchart of the study sample.
Abbreviation: PDSS-2, Parkinson's Disease Sleep Scale.

medication was converted to levodopa equivalent dose.[22] A movement disorders specialist performed a neurological examination to all participants. Thirty patients (12%) were evaluated at home due to the severity of their motor symptoms. PD patients were evaluated in the morning without antiparkinsonian medication for 12 hrs (off medication condition), using the Unified Parkinson's Disease Rating Scale (UPDRS)[23] and the modified Hoehn & Yahr Scale (H&Y).[24] Presence of motor fluctuations was identified by UPDRS-IV items 36, 37, and 38. After the assessment in off, patients took their usual first dose of antiparkinsonian medication and were re-evaluated 1 hr later (on medication condition), using the same instruments. Then, the Schwab and England Independence Scale (S&E) was applied regarding their state on and off.[25]

The Parkinson's Disease Sleep Scale (PDSS-2) was used to screen for sleep disturbances.[26] The applied cutoff score for clinically relevant sleep disturbances was PDSS-2≥18.[27]

All patients were tasked whether they had pain in the last month. Those who responded "yes" to the previous question were asked a series of questions regarding their pain: onset; duration; localization; features (including burning, tingling, formication, stabbing, aching, tension, tightness, or radiating); intensity; frequency; precipitating/relieving factors; temporal and topographical relationship with PD symptoms; and influence of motor complications, dyskinesias, and dopaminergic medication. Based on the patients' description, the neurologist categorized the pain, according to Ford framework,[17] as central parkinsonian pain, musculoskeletal pain, dystonia-related pain, radicular or neuropathic pain, and akathitic discomfort. Central parkinsonian pain was defined, according to Ford criteria,[17] as burning, tingling, formication, or "neuropathic" sensations, often relentless and bizarre in quality, not confined to root or nerve territory, and not explained by rigidity, dystonia, musculoskeletal, or internal lesion. The Brief Pain Inventory (BPI) was applied.[28]

The Hospital Anxiety and Depression Scale (HADS) was applied to measure anxiety and depression; a cutoff score of ≥8 was used for each subscale.[29] The SF-36 was used to evaluate the quality of life. Two summary scores, physical and mental health, were calculated with adjustment for the Portuguese population.[30]

Statistical analysis

Descriptive statistics were used for group characterization and non-parametric tests (ie, chi-square test, Fisher's exact test, and Mann–Whitney test) were applied for group comparisons. Simple and multiple logistic regression analyses were used to explore associations between the presence of sleep disturbances and subtypes of pain. The backward wald method was used for variable selection, with $p>0.100$ criterion for variable removal.

The threshold for statistical significance for group comparisons and for logistic regressions was $p<0.05$. The statistical analysis was conducted using the Statistical Package for the Social Sciences version 25.0 (SPSS, USA).

Results

Characteristics of the sample

Of the 229 PD patients examined, 122 (53%) were men, mean age was 69 years (sd=11), mean age at disease onset was 60 years (sd=12), and mean duration of the disease was 9 years (sd=6). Ninety-six (42%) were taking dopamine agonist (ie, 91 ropinirole, 2 pramipexole, 3 piribedil) and the mean levodopa equivalent dose was 900 mg/day (sd=542). The mean ropinirole dose was 10 (sd=5). Mean scores in motor scales were: 32 (sd=11) in UPDRSS-III off and 22 (sd=9) in on; 2.7 (sd=0.7) in H&Y off and 2.3 (sd=0.5) in on. One hundred and thirty-one (57%) had motor fluctuations. Mean in the functional independence scale S&E were 75 (sd=17) in off and 87 (sd=11) in on. At the time of the assessment, 162 patients (71%) reported pain. Of those with pain, 99 (61%) had musculoskeletal pain, 43 (27%) had dystonia-related pain, 38 (24%) had central parkinsonian pain, and 19 (12%) had radicular or neuropathic pain. No patient reported akathitic discomfort. The frequencies of HADS ≥8 on anxiety and depression subscales were, respectively, 102 (45%) and 111 (49%). Mean SF-36 summary scores for physical and mental health were, respectively, 40 (sd=11) and 46 (sd=12).

Characterization of sleep disturbances

Mean PDSS-2 total score was 15 (sd=10). One hundred and fifty-four (67%) patients scored PDSS-2<18 and 75 patients (33%) scored ≥18. Table 1 shows the demographic and clinical features of these patients. Patients with sleep disturbances (PDSS-2≥18) had more severe motor symptoms (UPDRS in off and on and H&Y in off), more motor fluctuations, lower functional independence (S&E in off and on), and were taking higher doses of antiparkinsonian medication ($p<0.05$). Patients with PDSS-2≥18 reported more frequent pain and greater pain intensity were more

Table 1 Demographic, clinical, and therapeutic characteristics of PD patients according to PDSS-2 total score

		PDSS-2		p
		<18 (n=154)	≥18 (n=75)	
Sex, men		87 (57%)	35 (47%)	0.162
Age (years)		69 (63–77)	71 (63–75)	0.830
Age at disease onset (years)		60 (53–70)	61 (53–67)	0.626
PD disease duration (years)		7 (4–11)	8 (5–14)	0.214
UPDRS III	Off	29 (22–36)	37 (29–45)	<0.001
	On	19 (14–26)	25 (19–32)	<0.001
H&Y	Off	2.5 (2–3)	3 (2–4)	0.006
	On	2 (2–2.5)	2.5 (2–2.5)	0.051
Motor fluctuations		78 (51%)	53 (71%)	0.004
S&E	Off	80 (70–90)	70 (50–80)	<0.001
	On	90 (80–90)	80 (70–90)	<0.001
Dopamine agonists		64 (44%)	29 (35%)	0.486
LED (mg/day)		700 (460–1040)	1,027 (600–1410)	0.001
Hypnotic medication				0.439
	No medication	56 (36%)	26 (35%)	
	BDZ	48 (31%)	22 (29%)	
	BDZ agonist	2 (1%)	0 (0%)	
	Tricyclic and tetracyclic antidepressants	14 (9%)	5 (7%)	
	Antipsychotic	5 (3%)	8 (11%)	
	Anticonvulsant	3 (2%)	1 (1%)	
	Other antidepressants	11 (7%)	7 (9%)	
	Combination of hypnotic medications	15 (10%)	6 (8%)	
Pain		101 (66%)	61 (81%)	0.014
BPI		23 (21–31)	34 (24–43)	<0.001
HADS	Anxiety ≥8	55 (36%)	47 (63%)	<0.001
	Depression ≥8	59 (38%)	52 (69%)	<0.001
SF-36	Physical health	42 (33–51)	32 (28–43)	<0.001
	Mental health	50 (41–57)	43 (34–49)	<0.001

Notes: UPDRS-III on, H&Y on, and S&E on were not applied to untreated patients. Data are presented as frequencies (%) and as medians (25th–75th percentiles). Chi-square test (or Fisher's exact when appropriate) and Mann–Whitney test were used for group comparisons.

Abbreviations: UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn & Yahr scale; S&E, Schwab and England Independence Scale; LED, Levodopa Equivalent Dose; BZD, Benzodiazepines; BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; SF-36, Short Form (36 itens) Health Survey.

anxious and depressed (HADS), and had poorer quality of life (SF-36 physical and mental health summary scores) than patients with PDSS-2<18. These two groups did not differ (p>0.05) regarding sex, age, age at disease onset, disease duration, and use of dopamine agonists (including type and dose) and hypnotic medication.

Sleep disturbances and subtypes of pain

The frequency of sleep disturbances was 20% for patients without pain and 38% for patients with pain (p=0.014). In comparison with patients without pain, the frequency of sleep disturbances was significantly higher for patients with central parkinsonian pain (53%, p=0.001), but not for musculoskeletal pain (32%, p=0.107), dystonia-related pain (37%, p=0.061), or radicular/neuropathic pain (26%, p=0.755).

Among patients with pain, a simple logistic regression revealed that the odds of having sleep disturbances were higher among patients with central parkinsonian pain (odds=2.25, 95% CI: 1.08–4.71; p=0.031). No significant association was found with musculoskeletal pain, dystonia-related pain, or radicular/neuropathic pain (Table 2). When adjusted for severity of motor symptoms in off (H&Y), presence of motor fluctuations, pain intensity (BPI), anxiety, and depression (HADS), the odds of having sleep disturbances remained higher in patients with central parkinsonian pain (adjusted odds=2.46, 95% CI: 1.06–5.74; p=0.037).

Discussion

In a series of 229 PD patients, the prevalence of sleep disturbances was 33% and of pain was 71%. The frequency of sleep disturbances is similar to another study that used PDSS-2≥18.[31] Although it is lower than other published series, with prevalence estimates of sleep disturbances ranging between 40% and 90%.[4,32] This wide variation is likely due to methodological differences (ie, assessment instruments and applied cutoffs). The prevalence of pain in our series is consistent with other cohorts of PD.[8,9,33]

Table 2 Odds of patients with pain (n=162) having PDSS-2 total score ≥18 according to pain subtypes

Subtype of pain	Odds	P	Adjusted odds*	p
Central parkinsonian	2.25	0.031	2.46	0.037
Musculoskeletal	0.56	0.080	-	-
Neuropathic	0.56	0.283	-	-
Dystonic	0.974	0.994	-	-

Notes: *The odds of having PDSS-2 total score ≥18 for each subtype of pain adjusted for H&Y off, motor fluctuations, BPI score, HADS – anxiety ≥8, and HADS – depression ≥8, with backward – wald selection method.

In accordance with a recent study,[15] PD patients with sleep disturbances had more severe motor symptoms, more anxiety and depression symptoms, lower functional independence, and poorer quality of life. As previously identified in other cohorts,[13,32] the intensity of pain among PD patients with sleep disturbances was significantly higher than in patients without clinically relevant sleep disturbances.

Presence of motor fluctuations was also more frequent among patients with sleep disturbances. Previous studies have demonstrated that motor fluctuations are more common in PD patients who report pain.[34–36] This pattern of findings raises the possibility that motor fluctuations may have a modulating effect on the relationship between pain and sleep.

The study results also demonstrate that the association between quality of sleep and pain in PD depends on pain subtype. Similar to other cohorts,[9,16,33,37] musculoskeletal and dystonia-related pain were the most common subtypes of pain. Although only central parkinsonian pain was significantly related to an increased risk of sleep disturbances, both in comparison to patients without pain and to patients with other pain subtypes. Patients with musculoskeletal pain or dystonia-related pain tended to have more sleep disturbances than patients without pain. However, among patients with pain, these pain subtypes were not related to an increased risk of sleep disturbances. The relationship between central parkinsonian pain and sleep disturbances was not statistically dependent on disease severity, presence of motor fluctuations, pain intensity, or mood symptoms.

Ford's classification of pain is specific for patients with PD and is based on the likely etiology of pain.[17] Even though it has been widely accepted,[38] Ford's criteria are not universally used and have not been thoroughly validated. This limits the comparison with other cohorts.

In the general population, several studies have shown that sleep deprivation leads to changes in pain processing with increased sensitivity to pain and a hyperalgesic effect,[39] whereas longer nocturnal sleeping time may reduce pain perception.[40] Persistent pain is also known to have a great impact on sleep and is one of the most frequent causes of sleep disturbances in older adults.[41,42] In a recent study, Krause et al[43] provided a central brain framework for the underlying impact of sleep loss in

pain. They demonstrated that acute sleep-deprivation amplifies pain reactivity within human primary somatosensory cortex, but blunts pain-reactivity in higher order valuation and decision-making regions of the striatum and insula cortex.

Both pain and sleep disturbances are known to involve brainstem structures and changes in neurotransmitter systems, namely dopamine.[44–46] The existing clinical evidence suggests an important role of the dopaminergic deficit in central parkinsonian pain[47] and it has been well demonstrated that dopamine contributes to the promotion and maintenance of arousal states and regulation of sleep and wakefulness.[11,48] The ascending reticular activating system, including parts of raphe nuclei which is a crucial sleep modulation center, has many dopaminergic receptors and pain induced alterations in dopaminergic system, that may deregulate raphe cells and contribute to long-term sleep loss.[44,45] Changes in the striatum and dopamine depletion are hallmarks of PD. However, the pathophysiological relationship between sleep and pain in PD is not yet understood.

The recruitment of participants to the study was consecutive. However, a significant number of subjects were unable to complete parts of the protocol due to cognitive impairment. The exclusion of participants with missing data set may have reduced the representativeness of the sample. The a priori exclusion of patients under advanced therapies for PD, namely deep brain stimulation, also reduces the representativeness of the sample, especially in the advanced stages of the disease. Another limitation of the study is the identification of sleep disturbances only by a self-report screening questionnaire, which is vulnerable to misrepresentation of the actual pattern and quality of sleep. As this study did not explore the characteristics of sleep disturbance, future studies ought to include polysomnographic recordings for further characterization and the level of arousal during the day should be taken into account. One major strength of this study is the diagnosis of PD and the clinical evaluation by movement disorders specialists, which reduces the risk of misdiagnosis.

In summary, sleep disturbances and pain are prevalent non-motor symptoms in PD. Poor quality of sleep is associated with more pain and more severe motor symptoms, anxiety, depression, and poorer quality of life. The study results revealed that the association between pain and sleep disturbances in PD appears to be dependent on the subtype of pain.

Conclusion

Patients with central parkinsonian pain are particularly prone to experience sleep disturbances. This relationship ought to be explored in future neurophysiological studies. A better understanding of the relationship between sleep disturbances and central parkinsonian pain may contribute to the development of new care strategies in PD patients.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Article III

Central Pain in Parkinson's disease: behavioral and cognitive characteristics

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Central Pain in Parkinson's disease: behavioral and cognitive characteristics

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Abstract

Introduction: Pain is a major non-motor symptom of Parkinson's disease (PD) and central parkinsonian pain is the core feature of the putative Park pain subtype of PD. This study aimed to explore the cognitive and behavioral profile of PD patients with central parkinsonian pain.

Material and Methods: A structured interview was used to identify and characterize pain in a cohort of 260 consecutive PD patients. The Ford classification of pain was applied. The Dementia Rating Scale-2 (DRS-2) and the Impulse Control Disorders in Parkinson's Disease Short Form (QUIP-S) were administered and patients' smoking habits were recorded. The Unified Parkinson's Disease Rating Scale (UPDRS) was used to assess motor and non-motor symptoms in *off* and *on* conditions.

Results:

One hundred and eighty-eight patients (68%) reported pain; and in 41 (22%) of them the pain was classified as central parkinsonian pain. PD patients with central parkinsonian pain had better cognitive performance in DRS-2 Initiation/Perseveration and Conceptualization subscales, but reported more other compulsive behaviors (e.g., hobbyism, punding, and walkabout) and had more current smoking habits than those without pain or with non-central parkinsonian pain. Multiple logistic regression analyses revealed that DRS-2 Conceptualization subscale, other compulsive behaviors, and smoking habits remained statistically associated with central parkinsonian pain even when other significant covariates were considered. Only patients with pain, regardless of type, had a gambling disorder.

Discussion: The study results provide further evidence that pain revealed that patients with central parkinsonian pain are more likely to present compulsive or addictive behaviors, despite having more preserved cognitive performance. Patients with central parkinsonian pain appear to have a distinct phenotype of PD.

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder that includes motor and non-motor symptoms, such as dementia, sleep disorders, autonomic dysfunction, sensory, and psychiatric symptoms[1]. It has been recognized that PD is highly heterogeneous, regarding clinical presentation and progression[2]. The emergence of patterns of co-occurrence or clustering of certain non-motor symptoms has led to the proposal of non-motor subtypes of PD [3, 4]. Sauerbier et al. has suggested seven specific non-motor symptom-dominant phenotypes, including a Park pain subtype[3]. It has been speculated that these different subtypes may have distinct pathogenesis[4].

Pain in PD is a major non-motor symptom with a prevalence of up to 85%, and is associated with poorer quality of life[5]. Central parkinsonian pain is believed to be the only subtype of pain that is directly related to the disease itself and is the core feature of the putative Park pain subtype[6]. Patients with central parkinsonian pain are known to be younger, have earlier disease onset, fewer comorbidities, greater non-axial motor symptom severity in *on*, more pain-related disability, more sleep disturbances, and more relief of pain with antiparkinsonian medication than patients with non-central parkinsonian pain[7, 8]. It is also widely recognized that younger patients with PD usually have more preserved cognition and are at higher risk of presenting impulse control disorders[9, 10].

The general aim of this study was to carry out a cognitive and behavioral characterization of PD patients with pain, specifically those with central parkinsonian pain.

Material and Methods

Participants

A cross-sectional study of PD patients was carried out in the Movement Disorders Clinic of Centro Hospitalar Universitário do Porto (CHUPorto). Full details of the protocol have been described in a previous article[7]. In brief, patients were eligible for inclusion if they met the United Kingdom Brain Bank criteria for diagnosis of PD [11]. Drug-induced parkinsonism, possible or probable

atypical parkinsonian syndromes, vascular parkinsonism, and advanced therapies (i.e., subcutaneous apomorphine pump, levodopa-carbidopa intestinal gel, or deep brain stimulation) were considered a priori exclusion criteria.

From a consecutive series of 322 possible subjects, 260 participated in the study (Figure 1). One patient refused to participate in the study and 53 were excluded before assessment (i.e., 13 moved geographically to a region not dependent from our center or could not be reached between inclusion and assessment, 4 could not be assessed due to logistic problems, 2 developed other debilitating conditions, 7 died, and 27 had less than three years of education) and 8 were excluded after the assessment (i.e., 3 due to inability to complete the Dementia Rating Scale-2 - DRS-2, 3 had a change in the diagnosis, and 2 due to incomplete data set).

All the patients (or legal representatives) were informed about the nature of the study and gave their written informed consent. The ethics committee of CHUPorto approved the study.

Procedures

A movement disorders specialist performed a semi-structured interview (supplementary material) and a neurological examination to all participants. PD patients were evaluated in the morning without antiparkinsonian medication for 12 hours (*off* medication condition), using the Unified Parkinson's Disease Rating Scale-III (UPDRS-III) [12]. After the assessment in *off* condition, patients took their usual first dose of antiparkinsonian medication and were re-evaluated one hour later (*on* medication condition), using the same instruments. UPDRS subscale for activities of daily living (UPDRS-II) was also applied regarding *off* and *on*. Levodopa responsiveness was calculated as the percent change in UPDRS score [i.e., (OFF − ON)/OFF*100]. All patients were asked whether they had pain in the last month. Those who responded "yes" to the previous question were asked a series of questions regarding their pain. Based on the patients' description, the neurologists categorized the pain, according to Ford framework[6], as central parkinsonian pain, musculoskeletal pain, dystonia-related pain, radicular or neuropathic pain, and/or akathitic discomfort. Central parkinsonian pain was defined, according to Ford criteria[6], as burning, tingling, formication, or "neuropathic" sensations, often relentless and bizarre in quality,

not confined to root or nerve territory, and not explained by rigidity, dystonia, musculoskeletal, or internal lesion. The neurologists used the Questionnaire for Impulse Control Disorders in Parkinson's Disease Short Form (QUIP-S) to identify participants with impulse control disorders (ICDs; i.e., gambling, sexual, buying, and eating behaviors), other compulsive behaviors (i.e., hobbyism, punding, and walkabout), and compulsive medication use [13, 14]. Patients' past and current smoking habits were recorded.

A trained neuropsychologist applied the Portuguese version of the DRS-2[15]. Test scores were adjusted for demographic characteristics (i.e., age and education) according to the national norms, and the fifth percentile of the norms was used as cut-off for cognitive impairment. DRS-2 was applied under the effect of the regular anti-parkinsonian medication (in *on* condition).

Statistical analysis

Descriptive statistics were used for group characterization and non-parametric tests (i.e., Chi-Square, Fisher's exact and Mann-Whitney) were applied for group comparisons. The threshold for statistical significance for group comparisons was $p<0.05$. Multiple logistic regressions explored group differences while considering relevant covariates. Backward selection method was applied with a threshold for variable removal of $p>0.100$. The statistical analysis was conducted using the Statistical Package for the Social Sciences version 25.0 (SPSS, USA).

Results

Total Sample

Of the 260 PD patients that were examined, 135 (52%) were men and 125 (48%) were women, with median age=70 years, education=4, age at disease onset=60 years, and disease duration=7 years. At the time of the assessment, 188 patients (68%) reported pain. Of those with pain, 41 (22%) had central parkinsonian pain and 147 (78%) had non-central parkinsonian pain. The demographic and clinical characteristics of the subgroups are presented in Table 1.

Central Parkinsonian Pain

As compared to patients without pain and patients with non-central parkinsonian pain, PD patients with central parkinsonian pain were younger at disease onset (respectively p=0.002 and p=0.011) and at assessment (respectively p=0.001 and p=0.002) and were taking more dopamine agonists (respectively p=0.031 and p=0.024) (Table 1). Patients with central and non-central parkinsonian pain had a higher UPDRS-II score in *off-state* than patients without pain (respectively p=0.001 and p=0.002). PD patients with central parkinsonian pain had greater UPDRS-II levodopa responsiveness than patients with non-central parkinsonian pain (p=0.001) and the responsiveness was higher than patients without pain although the level of statistical significance was marginal and non-significant (p=0.063).

PD patients with central parkinsonian pain had fewer deficits on DRS-2 Initiation/Perserveration (12%) and Conceptualization (2%) subscales than patients without pain (respectively 31%, p=0.028; and 22%, p=0.005) or with non-central parkinsonian pain (respectively 28%, p=0.039; 22%, p=0.004). No significant differences were found regarding DRS-2 Total score, Attention subscale, Construction subscale, and Memory subscale. Multiple logistic regressions revealed that patients with central parkinsonian pain had lower odds of having deficit on DRS-2 Conceptualization than patients without pain (adjusted Odds=0.08, 95%CI: 0.01, 0.82, p=0.034) or patients with non-central parkinsonian pain (adjusted Odds=0.12, 95%CI: 0.01, 1.00, p=0.050), when considering age, age at disease onset, agonist medication, and UPDRS-II levodopa responsiveness as covariates. The association between deficit on DRS-2 Initiation/Perseveration and central parkinsonian pain was no longer statistically significant when the same covariates were considered.

The frequency of positive symptoms on QUIP-S was not statistically different between patients with central parkinsonian pain (29.3%) and patients without pain (18.1%) or with non-central parkinsonian pain (25.2%). Though, the frequency of other compulsive behaviors (i.e., hobbyism, punding, and walkabout) was higher in patients with central parkinsonian pain (20%) than in patients with other subtypes of pain (8%, p=0.037), and in patients without pain although the level of statistical significance was marginal and non-significant (7%,

p=0.064). The odds of having other compulsive behaviors were higher for patients with central parkinsonian pain than with non-central pain (adjusted Odds=3.15, 95%CI: 1.00, 9.90, p=0.050), when considering age, age at disease onset, agonist medication, and UPDRS-II levodopa responsiveness as covariates. No patient without pain reported compulsive gambling, whereas 7% of patients with central parkinsonian pain or non-central parkinsonian pain had this ICD. No other specific ICDs were related to central parkinsonian pain.

PD patients with central parkinsonian pain (12%) had more current smoking habits than patients without pain (1%, p=0.023) or with non-central parkinsonian pain (3%, p=0.043). The odds of having current smoking habits were higher for patients with central pain than patients without pain (adjusted Odds=6.58, 95%CI: 0.71, 61.38, p=0.098), though the level of statistical significance was marginal and non-significant when age, age at disease onset, agonist medication, and UPDRS-II levodopa responsiveness were considered. The comparison with patients without pain was no longer statistically significant when the same set of covariates were considered.

Discussion

The present study revealed that patients with central parkinsonian pain had more compulsive behaviors and addictive habits than patients without pain or with non-central parkinsonian pain, despite having more preserved cognitive performance.

In our cohort, pain was not related to increased cognitive deficits in the DRS-2. Even though, in non-PD populations, chronic pain has been linked to impairments in memory, attention and executive functions[16-18] and to an accelerated memory decline and increased probability of dementia[19]. In PD populations, the association between pain and cognitive dysfunction is less clear. There are reports of negative findings[20], but there are also studies that found significant associations between these two non-motor symptoms in PD[21, 22]. The low sensitivity of DRS-2 to mild deficits and small differences in cognitive functioning can potentially explain the non-significant difference between patients without pain and those with non-central parkinsonian pain in our cohort. Interestingly, PD patients with central parkinsonian pain had better cognitive

performance in the Initiation/Perseveration and Conceptualization subscales than patients without pain or with non-central parkinsonian pain. These DRS-2 subtests measure executive functions and verbal intelligence[23] and are predictive of dementia in PD[23-25]. This finding suggests that having a more preserved cognition may be a characteristic of the putative Park pain subtype of PD. Noteworthy cognition was assessed under the effects of antiparkinsonian medication. The central parkinsonian pain is believed to be related to a dopaminergic deficit and there are reports of a greater relief of pain with antiparkinsonian medication than in other types of pain[7, 8].

In our cohort, patients with central parkinsonian pain had more current smoking habits than patients without pain or with non-central parkinsonian pain. However, the frequency of past smoking habits was not different between these groups of PD patients. Epidemiological studies have consistently reported an inverse correlation between tobacco use and PD[26, 27]. There is evidence of a functional interaction between dopamine and nicotinic cholinergic systems and that nicotine may contribute to the symptomatic management of non-motor symptoms in PD, by stimulating the dopamine release in the striatum[28, 29] . Several studies suggest that nicotine may modulate the nociceptive experience in non-PD patients. So, it is reasonable to speculate that the more frequent current smoking addiction in patients with central parkinsonian pain may be related to a greater and more sustained responsiveness to nicotine.

In our cohort, 5% of all PD patients experienced pathological gambling. This frequency is consistent with the literature. It has been observed that pathological gambling occurs more frequently in PD patients (3.4–6.1%) than in the general population (0.25–2%)[30]. Though only patients with pain, regardless of the type, reported pathological gambling in our cohort. This finding is consistent with the notion that patients with pain may be more vulnerable to pathological gambling than patients without pain[31, 32]. It has been hypothesized that the inability to cope with painful or uncomfortable physical sensations may drive the gambling behavior, due to a general inability to cope with discomfort. Patients with central parkinsonian pain also reported more other compulsive behaviors (e.g., hobbyism, punding, and walkabout) than patients without pain or with other pain subtypes.

The pathological mechanisms of ICDs in PD are not yet fully understood but it has been argued that in PD the dysregulation of two important dopaminergic circuits, the mesolimbic and mesocortical pathways, leads to the clinical manifestation of impulsive and compulsive behaviors[9]. In accordance, neurofunctional studies have found increased functional activation and dopamine release in regions associated with the mesolimbic reward system in PD patients with ICD[33]. In recent years there has been increasing evidence of the involvement of the mesolimbic system in acute and chronic pain[34]. Chronic pain states may induce changes in neuronal plasticity and functional connectivity in several parts of the brain reward center, including nucleus accumbens, the ventral tegmental area and the prefrontal cortex[35]. Several studies suggest that the mesolimbic dopamine system modulates the perception of nociceptive information, the efficacy of pain medications, and the affective symptoms of chronic pain[35].

Patients with central parkinsonian pain were younger, took more dopamine agonists, and presented greater responsiveness to levodopa on activities of daily living (as measured by UPDRS-II) than patients without pain or with other types of pain. It can be argued that the behavioral and cognitive features of patients with central parkinsonian pain can be explained, at least in part, by these demographic and clinical characteristics of the patients. In other words, the associations between pain and other non-motor symptoms may reflect shared protective and risk factors, in addition to possible common pathophysiological mechanisms. Supporting this hypothesis is the reported association between poor quality of sleep and both central parkinsonian pain[8] and ICDs[36] in PD. We observed in the present study that patients with central parkinsonian pain had more preserved cognition. Concurrently a slower cognitive decline, especially in frontal-lobe related functions, has been described in PD patients with ICDs[37]. Patients with central parkinsonian pain appear to have a distinct phenotype of PD.

One major strength of this study is the diagnosis of PD and the clinical evaluation by movement disorders specialists, which reduces the risk of misdiagnosis, and the neuropsychological evaluation performed by an experienced neuropsychologist in the assessment of PD patients. The limitations of the study include the *a priori* exclusion of patients under advanced therapies

for PD, namely deep brain stimulation, which reduces the representativeness of the sample, especially in the advanced stages of the disease. The QUIP-S and DRS-2 are recommended by the International Parkinson's and Movement Disorder Society[14] to screen for ICDs and cognitive deficits in PD. These instruments have respectively low specificity and low sensitivity. Not all individuals positive for ICDs on QUIP-S meet the diagnostic criteria and patients with normal DRS-2 may have cognitive deficits not detected by the instrument.

In summary, patients with central parkinsonian pain are more likely to present certain compulsive and addictive behaviors than patients without pain or with non-central pain, even though they appear to have more preserved cognition. These findings provide support to the existence of a Park pain phenotype.

Data availability

Database of Centro Hospitalar e Universitário do Porto, Portugal

Author's Roles

Authors NVC, SC, AM, AG, ALF and JMCL were involved in the project conception. Authors NVC, SC, AM and AG organized the project. Authors NVC, SC, AM, AG, IM, JF and JD were involved in project execution. Author SC designed and executed the statistical analysis. Author NVC drafted the manuscript. All authors reviewed the manuscript.

Relevant conflicts of interests/financial disclosures: Nothing to report

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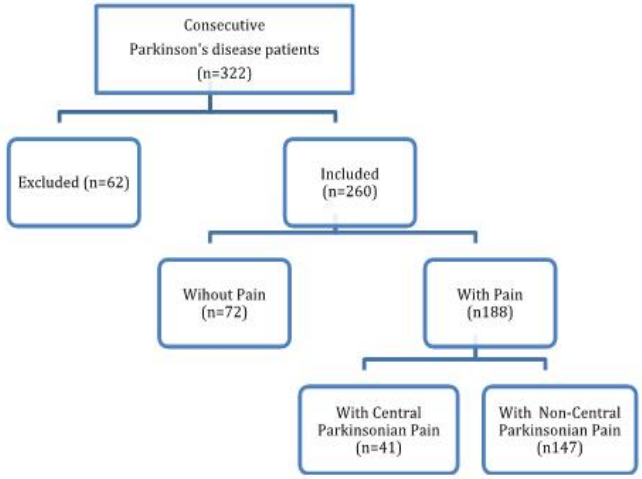

Figure 1. Flowchart of the study sample

Table 1. Demographic, clinical, and therapeutic characteristics of Parkinson's disease patients according to pain subtype

		A- PD without pain (n=72)	B- PD with non-central pain (n=147)	C- PD with central pain (n=41)	*P*		
					A vs. B	A vs. C	B vs. C
Sex - male		44 (61%)	73 (50%)	18 (44%)	0.111	0.077	0.514
Age		72 (64-78)	70 (63-77)	64 (56-71)	0.556	**0.001**	**0.002**
Education		4 (4-9)	4 (4-6)	4 (4-9)	0.254	0.977	0.396
Age at disease onset		63 (55-69)	60 (53-69)	57 (45-63)	0.291	**0.002**	**0.011**
Disease duration (years)		6 (4-13)	8 (4-12)	6 (4-12)	0.030	0.815	0.093
UPDRS-II	OFF	11 (7-17)	15 (9-23)	18 (12-22)	**0.002**	**0.001**	0.274
	ON	6 (3-11)	9 (6-13)	8 (4-11)	**0.002**	0.108	0.360
UPDRS-II levodopa responsiveness		44 (20-63)	36 (19-52)	56 (43-67)	0.156	0.063	**0.001**
UPDRS-III	OFF	30 (22-38)	32 (25-41)	34 (23-42)	0.118	0.122	0.572
	ON	21 (15-26)	21 (16-27)	24 (17-30)	0.481	0.112	0.250
UPDRS-III levodopa responsiveness		32 (22-38)	31 (22-42)	30 (23-42)	0.844	0.766	0.645
L-Dopa Equivalent (mg)		710 (400-1063)	840 (500-1180)	880 (580-1160)	0.060	0.170	0.974
Agonists		27 (38%)	57 (39%)	24 (59%)	0.855	**0.031**	**0.024**
Pain treatment							
	NSAIDs	-	41 (28%)	9 (22%)	-	-	0.447
	Anti-depressant	-	4 (3%)	4 (10%)	-	-	0.070
	AEDs	-	6 (4%)	4 (10%)	-	-	0.229
	Paracetamol	-	30 (20%)	11 (27%)	-	-	0.379
	Other drugs	-	14 (10%)	2 (5%)	-	-	0.529
DRS-2	Total	25 (35%)	54 (37%)	11 (27%)	0.771	0.387	0.238
	Attention	21 (29%)	46 (31%)	11 (27%)	0.748	0.791	0.582
	Initiation/ Perseveration	22 (31%)	41 (28%)	5 (12%)	0.682	**0.028**	**0.039**
	Construction	21 (29%)	39 (27%)	11 (27%)	0.681	0.791	0.969
	Conceptualization	16 (22%)	32 (22%)	1 (2%)	0.939	**0.005**	**0.004**
	Memory	19 (26%)	36 (25%)	10 (24%)	0.761	0.815	0.990
QUIP - S	Total	13 (18%)	37 (25%)	12 (29%)	0.239	0.167	0.597
	Gambling	0 (0%)	10 (7%)	3 (7%)	**0.033**	**0.046**	>0.999
	Sexual	4 (6%)	15 (10%)	2 (5%)	0.251	>0.999	0.372
	Buying	4 (6%)	5 (3%)	3 (7%)	0.480	0.703	0.375
	Eating	5 (7%)	9 (6%)	1 (2%)	0.777	0.414	0.693
	Other Coumpulsive Behaviors	5 (7%)	11 (8%)	8 (20%)	0.886	0.064	**0.037**
	Compulsive Medication Use	1 (1%)	6 (4%)	0 (0%)	0.287	>0.999	0.342
Smoking	Current Habits	1 (1%)	5 (3%)	5 (12%)	0.666	**0.023**	**0.043**
	Past Habits	14 (19%)	35 (24%)	10 (24%)	0.451	0.537	0.956

PD: Parkinson's disease; UPDRS: Unified Parkinson's Disease Rating Scale; NSAIDs: Non-steroidal anti-inflammatory drugs; AEDs: Anti-epileptic drugs; DRS: Dementia Rating Scale; QUIP-S: Impulse control disorders in Parkinson's disease short form.
Data are presented as frequencies (%) and medians (25^{th}-75^{th}). Chi square (or Fisher's exact when appropriate) and Mann-Whitney test were applied for group comparisons.

Semi-structured questionnaire for pain

Do you have pain?

Yes __ No ___

(If yes, continue the questionnaire)

Characteristics

Burning__ Aching ____ Cramping____ Tingling____ Sense of restlessness___

Other _____

Duration

<1 month ___ 1 - 3 months ___ 3 months - 1 year ___ More than 1 year____

Age of onset ___

Localization ____

Frequency

Continuous (always/every day) ___

Recurrent (several days a week to several days a month) ___

Sporadic (less than a few days a month) __

Intensity

Mild___ Moderate___ Intense ____

Aggravating Factors

Movement ___ Rest ____ Temperature change ___

Other _____

Relief Factors

Movement ___ Rest ____ Temperature change ___

Other _____

Drugs **Dosis**

Amitriptyline _____

Gabapentin _____

Pergabalin _____

Venlafaxine _____

Paracetamol _____

NSAIDs (_____) _____

COX inhibitor _____

Tramadol _____

Other (____) _____

Relief with medication

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

1

Alternative Therapeutics

No_ Acupuncture__ Massages__ Meditation___ "Natural" Pharmacies ___

Other ____

Relief with alternative therapeutics

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Satisfaction with pain management

Unsatisfied __ Slightly Satisfied __ Moderately satisfied __ Very satisfied ___

Relationship with Parkinson's Disease

Do you think it is related to PD? No____ Yes_____

Before start of PD_____ After start of PD _____

Topographical relation to PD? No____ Yes_____

Relation to dystonia? No ____ Yes _____

Does it improve with anti-parkinsonian medication? No ____ Yes_____

Relation with dyskinesias? No ____ Yes __

Does it worsen with anti-parkinsonian medication? No ____ Yes _____

Does the pain have fluctuations? No ____ Yes _____

What time of day do you have the most pain?

Morning _____ Afternoon _____ Night ___ Early morning ____

Neurological exam

Motor or sensory signs of nerve or root entrapment? Yes ___ No___

Changes other than extrapyramidal signs _____

Classification of pain (see Table 1)

Table 1 *Clinical classification of painful or unpleasant sensations in PD*

Category by description	Clinical features	Check
Musculoskeletal	Aching, cramping, arthralgic, myalgic sensations in joints, and muscles; Associated findings may include muscle tenderness, arthritic changes, skeletal deformity, limited joint mobility, postural abnormalities, and antalgic gait; May be exacerbated by parkinsonian rigidity, stiffness, and immobility, and relieved by mobility; May fluctuate with medication dosing, and improve with levodopa	
Dystonic	Associated with sustained twisting movements and postures; Muscular contractions often very forceful and painful; Dystonia may involve any limb or extremity, as well as facial and pharyngeal musculature; May fluctuate closely with medication dosing: early morning dystonia, off dystonia, beginning-of-dose and end-of-dose dystonia, peak dose dystonia	
Radicular/neuropathic	Pain in a root or nerve territory, associated with motor or sensory signs of nerve or root entrapment	
Central parkinsonian pain	Burning, tingling, formication, "neuropathic" sensations, often relentless and bizarre in quality, not confined to root or nerve territory; Pain may have an autonomic character, with visceral sensations or dyspnea, and vary in parallel with the medication cycle as a non-motor fluctuation. Not explained by rigidity, dystonia, musculoskeletal or internal lesion	
Akathisia	Subjective sense of restlessness, often accompanied by an urge to move. May fluctuate with medication effect, and improve with levodopa	

From: Ford, B., *Pain in Parkinson's disease.* Mov Disord, 2010. 25 Suppl 1: p. S98-103.

CHAPTER V | Summary of findings

Summary of findings

Main Findings

The main findings of this thesis can be outlined as follows:

Aim 1. To determine the prevalence and characteristics of pain and pain subtypes in PD

Hypotheses: Pain is a common non-motor symptom and musculoskeletal pain is the most frequent subtype of pain. Central parkinsonian pain prevalence is around 15%. Pain in PD is intense and causes disability.

Presented in the Article I

Summary of findings: In our study, 73% (n=212) of PD patients had pain. Sixty-three percent had musculoskeletal pain, 27% had dystonic pain, 22% had central parkinsonian pain and 9% had radicular/neuropathic pain. No patients had akathisia. Among PD patients with only one subtype of pain (n=165), 21% had central parkinsonian pain and 79% had non-central parkinsonian pain (56% musculoskeletal pain, 13% radicular/neuropathic pain and 10% dystonia-related pain). In 32% of the patients pain appeared before the motor symptoms. Pain had a median duration of 5 years and 78% of the patients had pain for more than 1 year. In 63% of the patients, the pain was constant, in 28% it was intermittent, and in 9% it was sporadic. Most PD patients classified the pain as moderate (60%); 16% considered it severe and 24% rated it as mild. The average BPI severity and interference scores were 13 and 27, respectively, and the average PDI score was 23. Higher BPI severity and interference scores and PDI scores were related to female sex, osteoarticular pathologies, non-tremoric motor phenotype, anxiety and depression.

Aim 2. To explore the demographic and clinical predictors of pain in PD

Hypotheses: PD patients with central parkinsonian pain have distinctive demographic and clinical features.

Presented in the Article I

Summary of findings: PD patients with pain, regardless of subtype, had greater severity of motor symptoms, higher frequency of motor fluctuations, longer duration of the *off* stage, and took a higher dose of antiparkinsonian drugs. These patients had less functional independence and more comorbidities. Patients with predominantly tremorous motor phenotype were less likely to have pain than patients with akinetic-rigid or mixed motor phenotype.

Patients with central parkinsonian pain were younger and had an earlier onset of the disease, less comorbidities, lower pain frequency before the onset of motor symptoms, and more disability.

Aim 3. To investigate the relationship between pain and central parkinsonian pain, and other symptoms in PD, both motor and non-motor

Hypotheses: PD patients with pain and central parkinsonian pain have more severe motor symptoms. PD patients with central parkinsonian pain have a specific pattern of non-motor symptoms (e.g., sleep, depression, anxiety, impulse control, smoking habits, and cognitive function).

Presented in the Article I, Article II and Article III

Summary of findings:

a. Motor symptoms (Presented in the Article I and Article III)
   Patients with central parkinsonian pain had more UPDRS-II symptoms in *off* than patients without pain. Patients with central parkinsonian pain had more

severe non-axial motor symptoms in *on*, but a lower stage of the disease as measured by H&Y in *on*. No significant differences were found regarding UPDRS-III in *on*, S&E in *off* and *on*, FOG-Q, motor phenotype, axial index in *off* and *on*, motor fluctuations or dyskinesia.

b. Sleep Disturbances (Presented in the Article II)

The frequency of sleep disturbances was 20% for patients without pain and 38% for patients with pain ($p<0.05$). The intensity of pain among PD patients with sleep disturbances was significantly higher than in patients without sleep disturbances. The frequency of sleep disturbances was significantly higher for patients with central parkinsonian pain (53%) but not for musculoskeletal pain, dystonia-related pain, or radicular/neuropathic pain. Among patients with pain, the odds of having sleep disturbances were higher in patients with central parkinsonian pain (OR 2.25).

c. Anxiety and depression (Presented in the Article I)

The frequency of anxiety was 36% for patients without pain and 50% for patients with pain ($p<0.05$). The frequency of depression was 44% for patients without pain and 52% for patients with pain ($p>0.05$). No differences were found in anxiety and depression in PD patients with central parkinsonian and other subtypes of pain.

d. Impulse Control Disorders and Addictive Behaviors (Presented in the Article III)

The frequency of ICDs was 18% for PD patients without pain, 26% for PD patients with non-central parkinsonian pain and 29% in PD patients with central parkinsonian pain (not statistically different). All 13 patients with pathological gambling had pain. Other compulsive behaviors (i.e., hobbyism, punding, and walkabout) were more frequent in patients with central parkinsonian pain (20%) than in PD patients with non-central pain (8%) ($p<0.05$).

The total frequency of past smoking habits was 22.7% and current smoking habits was 3.5%. PD patients with central parkinsonian pain (12%) had more current smoking habits than patients without pain (1%) or with non-central parkinsonian pain (3%) ($p<0.05$).

e. Cognition (Presented in the Article III)

PD patients with central parkinsonian pain had fewer deficits on DRS-2 Initiation/Preservation (12%) and Conceptualization (2%) subscales than patients without pain (31% and 22%, respectively) or with non-central parkinsonian pain (28% and 22%, respectively). In the performance on DRS-2 Total scale, the frequency of impaired performance was: 27% on PD patients with central parkinsonian pain, 37% on PD patients with non-central pain and 35% on PD patients without pain had impaired cognitive function (not statistically different).

Aim 4. To investigate the relationship of central parkinsonian pain and antiparkinsonian treatments

Hypothesis: The central parkinsonian pain improves with antiparkinsonian treatment.

Presented in the Article I

Summary of findings: PD patients with central parkinsonian pain had greater pain relief with antiparkinsonian medication. Pain relief with antiparkinsonian medication remained significantly associated with central parkinsonian pain and the presence of motor fluctuations.

Aim 5. To put forward a clinical characterization of the PD subtype Park pain

Hypothesis: Park pain subtype is characterized by unique clinical features.

Presented in the Article I, Article II and Article III

Summary of findings: The Park pain subtype can be clinically characterized by the presence of central parkinsonian pain in a younger PD patient with earlier disease onset, more severe non-axial symptoms, more preserved executive functions, more sleep disturbances, more compulsive behaviors (punding, hobbyism, walkabout or hoarding), more current smoking habits, and an important pain-related disability. Patients with PD and central parkinsonian pain had a greater pain relief with optimization of antiparkinsonian medication independent of motor status.

CHAPTER VI | General discussion

General discussion

Pain in Parkinson's Disease

This study confirms that pain is a major disturbing non-motor symptom in PD patients. The prevalence of pain was high in PD patients and the most common pain subtype is musculoskeletal. These results are consistent with other cohorts of patients with PD[113-115].

Interestingly, one third of PD patients with pain referred the appearance of this symptom prior to the onset of motor manifestations which could correspond to the prodromal stage of PD[160]. As previously described, multiple nervous structures are involved in the pathophysiology of pain at the pre-motor stage of the disease and may suffer neurodegeneration prior to the substantia nigra that causes the motor symptoms[32]. The presence of pain was found to be related to more severe motor symptoms. These findings support previous reports of significant associations between pain and more severe motor manifestations of PD[143,167].

Regarding the relationship of pain with other non-motor symptoms, the intensity of pain among PD patients with sleep disturbances was significantly higher than in patients without sleep disturbances, as previously identified in other PD cohorts[182,274].

The presence of pain, as expected, was significantly related to anxiety [184]. However, the frequency of depression was not statistically higher among patients with pain, is different from other studies[275,276].

In our cohort, 5% of all PD patients experienced pathological gambling. This frequency is consistent with the literature. The estimated occurrence of pathological gambling in PD patients (3.4–6.1%) is higher than in the general population (0.25–2%)[277]. Interestingly only patients with pain, regardless of the type, reported pathological gambling in our cohort. This finding is consistent with the notion that patients with pain may be more vulnerable to pathological gambling than patients without pain[278,279]. It has been hypothesized that the inability to cope with painful or uncomfortable physical sensations may drive the gambling behavior, due to a general inability to cope with discomfort.

In our cohort, pain was not related to increased cognitive deficits in a screening measure (i.e., the DRS-2). Although in non-PD populations, chronic pain has been linked to impairments in memory, attention and executive functions[280-282] and to accelerated memory decline and an increased probability of dementia[283] in PD patient populations the association between pain and cognitive dysfunction is less clear. There are reports of a non-association between pain and cognitive decline in PD patients with pain[284], but there are also studies that found significant associations between these two non-motor symptoms in PD[118,276,285].

Central parkinsonian pain

The prevalence of central parkinsonian pain (21%) in our cohort is somewhat higher than in other studies[113-115,117]. This variability could be related to differences in sample size, patient selection procedures, and reliability of the classification. Patients with central parkinsonian pain were younger at the time of the assessment and at disease onset. This association between central parkinsonian pain and earlier onset of PD is consistent with another study[143]. Patients with central parkinsonian pain appear to have more non-axial levodopa-resistant symptoms and more pain-related disability than patients with other subtypes of pain despite having similar or even less severe axial symptoms. One interesting finding is that medical comorbidities, including osteoarticular disorders, were less frequent among patients with central parkinsonian pain. In our opinion, these results provide support to the notion that central parkinsonian pain is a manifestation of PD[119] and the hallmark of the putative Park pain subtype.

Central parkinsonian pain and others non-motor symptoms

Central parkinsonian pain was significantly related to an increased risk of sleep disturbances, both in comparison to patients without pain and to patients with other pain subtypes. The relationship between central parkinsonian pain and sleep disturbances was not statistically dependent on disease severity, presence of motor fluctuations, pain intensity or mood symptoms. Pain and sleep disturbances are known to involve the same brainstem structures and changes in the same neurotransmitter systems, namely dopamine[286-288]. The existing clinical evidence

suggests an important role of dopaminergic deficits in central parkinsonian pain and it has been well demonstrated that dopamine contributes to the promotion and maintenance of arousal states and regulation of sleep and wakefulness[181,289]. The ascending reticular activating system, including parts of the raphe nuclei which is a crucial sleep modulation center, has many dopaminergic receptors and pain-induced alterations in the dopaminergic system may deregulate raphe cells and contribute to long-term sleep loss[286,287].

Anxiety and depression symptoms were not significantly different between patients with central versus non-central parkinsonian pain. These negative findings suggest that the association between pain and depression is weaker and even more complex in PD than in other non-PD populations[290] partly because both can be a non-motor manifestation of the disease.

Patients with central parkinsonian pain reported more other compulsive behaviors (e.g., hobbyism, punding, and walkabout) than patients without pain or with other pain subtypes. It is worth noting that no significant association was found with ICDs, other than pathological gambling, which was not specific to central parkinsonian pain. The pathological mechanisms of ICDs in PD are not yet fully understood but it has been argued that in PD the dysregulation of two important dopaminergic circuits, the mesolimbic and mesocortical pathways, leads to the clinical manifestation of impulsive and compulsive behaviors[83]. Neurofunctional studies have found increased functional activation and dopamine release in regions associated with the mesolimbic reward system in PD patients with ICDs[291] and there has been increasing evidence of the involvement of the mesolimbic system in acute and chronic pain[202,292].

In our cohort, patients with central parkinsonian pain had more current smoking habits than patients without pain or with non-central parkinsonian pain. However, the frequency of past smoking habits was not different between these groups of PD patients. Epidemiological studies have consistently reported an inverse correlation between tobacco use and PD[18,293]. There is evidence of a functional interaction between dopamine and nicotinic cholinergic systems and it is known that nicotine may contribute to the symptomatic management of non-motor symptoms in PD by stimulating dopamine release in the striatum[294,295]. Several

studies suggest that nicotine may modulate the nociceptive experience in non-PD patients. Thus, it is reasonable to speculate that the higher frequency of current smoking habits in patients with central parkinsonian pain is related to a greater and more sustained responsiveness to nicotine.

Interestingly, PD patients with central parkinsonian pain had better cognitive performance in the Initiation/Perseveration and Conceptualization subscales than patients without pain or with non-central parkinsonian pain. These DRS-2 subtests measure executive functions and verbal intelligence[296] and are predictive of dementia in PD[296-298]. This finding suggests that preserved cognition may be a characteristic of the putative Park pain subtype of PD. It is important to note that cognition was assessed under the effects of antiparkinsonian medication. Central parkinsonian pain is believed to be partially related to a dopaminergic deficit and there are reports of a greater pain relief with antiparkinsonian medication than with other types of pain[299,300].

Patients with central parkinsonian pain were younger, took more dopamine agonists, and presented greater responsiveness to levodopa on activities of daily living (as measured by UPDRS-II) than patients without pain or with other types of pain. It can be argued that the behavioral and cognitive features of patients with central parkinsonian pain can be explained, at least in part, by these demographic and clinical characteristics of the patients. In other words, the associations between pain and some non-motor symptoms may reflect shared protective and risk factors, in addition to possible common pathophysiological mechanisms.

Almost all patients with central parkinsonian pain reported relief of pain with dopaminergic therapy. This greater responsiveness to dopaminergic treatment was independent of motor fluctuations. These results provide support to the notion that abnormal sensory detection in PD patients can be improved with dopamine therapy, especially in patients with central parkinsonian pain[160,204]. It is still unclear whether dopamine has a real antinociceptive effect or only a modulatory effect on pain[148]. These data points to the need for adjustments in dopaminergic therapy when pain is an important and debilitating symptom irrespective of the motor state, in particular for patients with central parkinsonian pain.

Park pain subtype

PD is a heterogeneous disease and patients with PD present and progress in different ways and because of that it has been speculated that there are different subtypes of PD[100]. The identification of these subtypes may be useful in providing a more accurate diagnosis, treatment and prognosis for individual patients in clinical practice and in helping to stratify subgroups for clinical trials[301]. The specific clinical characteristics of each non-mor subtype are elucidated by cohort studies, such as the present one[105]. One of the subtypes recognized in PD is Park pain[103]. We believe that our work can help define the clinical features of the Park pain subtype. The main clinical feature and the *sine qua non* condition of the Park pain subtype is the presence of central parkinsonian pain. PD patients with central parkinsonian pain are younger, have an earlier disease onset, more severe non-axial symptoms, more preservation of executive functions, more sleep disturbances, more compulsive behaviors (punding, hobbyism, walkabout or hoarding), and more current smoking habits. PD patients with central parkinsonian pain report important pain-related disability, but great pain relief with optimization of antiparkinsonian medication.

Implications for clinical practice

1. Pain should be recognized as a common feature of PD.

2. Clinicians should proactively diagnose pain in PD patients.

3. It is important to correctly classify the pain subtype in PD patients.

4. Central parkinsonian pain is unique to PD.

5. Central parkinsonian pain has distinctive demographic and clinical characteristics.

6. The Park pain subtype can be clinically characterized by the presence of central parkinsonian pain in a younger PD patient with earlier disease onset, more severe non-axial symptoms, more preservation of executive functions, more sleep disturbances, more compulsive behaviors (punding, hobbyism, walkabout or hoarding), more current smoking habits, and an important pain-related disability.

7. Central parkinsonian pain is difficult to treat, requires an interdisciplinary approach and clinicians should ensure that patients have optimal dopaminergic therapy.

Implications for future and for research

1. It is necessary to establish a widely accepted definition of pain in PD.

2. A standardized assessment protocol needs to be developed to evaluate central parkinsonian pain in PD.

3. The clinical features of the Park pain subtype that were put forward ought to be confirmed in future studies with other cohorts of PD patients.

4. Further basic science research should be conducted to determine if a common pathophysiological mechanism underlies different non-motor symptoms constituting the Park pain subtype.

5. Future studies should clarify the role of non-dopaminergic treatments (e.g., non-steroidal analgesics, antidepressants or antiepileptic drugs) and deep brain surgery in the treatment of central parkinsonian pain.

Strengths and Limitations

The main strength of this research is the comprehensive approach to the study of central parkinsonian pain, the one pain subtype etiologically caused by PD and the core feature of the putative Park pain subtype. Most previously published studies addressed PD pain in a general sense and did not differentiate between pain subtypes.

Another important strength is that the thesis is based on an extensive study of a large cohort of PD patients evaluated by movement disorders specialists and neuropsychologists highly experienced in following PD patients. This minimizes common problems in cross-sectional assessment studies in PD, such as the possibility of misdiagnosis (mainly in the initial phases of the disease) and the misuse of specific instruments by inexperienced technicians. Another important strength of this study is that the patients in our cohort were evaluated in both *on* and *off* conditions, which is another specific and unique characteristic of PD. An evaluation based only on the clinical history would not have allowed us to notice all the differences, namely motor, between these two conditions. To ensure a representative sample of the entire population and to avoid losses as much as possible, patients with severe motor symptoms that rendered it difficult to conduct an evaluation at the hospital, were evaluated at home.

This research has some limitations. First, the observational study was performed in a cohort of patients with PD from a single center, limiting its external validity. The consecutive nature of the recruitment, the extremely high acceptance rate, and the large sample size decreased potential selection biases in our study. Although a hospital-based sample may not be perfectly representative of the whole PD patient population, our Movement Disorders Outpatient Clinic, as part of the National Health Service with universal coverage, receives PD patients in all stages of the disease. Therefore, we expect that the present study findings would be similar to a population-based study. Second, the heterogeneity of the subtypes of PD pain was not completely addressed in this study, even though some pain subtypes classified as non-central parkinsonian pain may be related (directly or indirectly) to PD. During the study development, a new scale for pain in PD – the *King's*

Parkinson's Disease Pain Scale - was proposed[302]. This scale includes 7 domains out of a total of 14 items that allow for the classification of the frequency and severity of pain, but it does not allow a syndromic classification. This scale is recommended for pain intensity assessment by the Movement Disorders Society[141,303]. In future studies, this classification must be considered.

CHAPTER VII | Conclusion

Conclusion

This thesis provides a comprehensive and original approach to pain in PD. Our research indicates that pain in PD is a major and heterogeneous non-motor symptom. Central parkinsonian pain, the hallmark of the putative Park pain subtype, has unique features and is related with distinct demographic and clinical characteristics.

The research that constitutes this PhD thesis is expected to provide an important scientific impetus and interest in the study of central parkinsonian pain. In the future, it will be essential to establish a standard assessment protocol and develop strategies to prevent and treat central parkinsonian pain.

To conclude with a personal note, my clinical practice with PD patients triggered my search for answers on a disabling symptom in PD – pain, and sustained my pursuit for clues on how to alleviate it. This study helped me to better understand the loss of quality of life that patients with PD suffer from having pain. Also, it has allowed me to develop valuable skills that will be useful to improve my clinical practice and to continue my investigation on the non-motor symptoms in PD.

CHAPTER VIII | References

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