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CHRONIC PAIN IN PARKINSON'S DISEASE: CLINICAL AND PATHOPHYSIOLOGICAL ASPECTS

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CHRONIC PAIN IN PARKINSON'S DISEASE: CLINICAL AND PATHOPHYSIOLOGICAL ASPECTS

Abstract

Pain is an increasingly recognized non-motor symptom of Parkinson's disease (PD), with significant prevalence and strong impact on quality of life of patients. Moreover, pain can occur with various features in PD and several subtypes may coexist in a same patient, leading to a complex presentation and difficult diagnosis and treatment. In this paper we review the clinical manifestations of painful phenomena in PD, with focus on classifications and algorithms allowing to standardize the diagnosis of pain and PD. We also discuss the pathophysiological mechanisms underlying pain in PD, particularly parkinsonian central pain, in regard to recent clinical, neurophysiological and imaging studies.

Keywords: Pain, Parkinson's disease, central, nociceptive

Introduction

Non-motor symptoms of Parkinson's disease (PD) are increasingly recognized, and among them pain is a frequent and debilitating manifestation of the disease. Painful experiences can occur with various features in PD and hereby are difficult to describe by patients and by clinicians. Moreover, several types of pain may coexist in one patient, leading to insufficient identification and treatment of pain. Efforts have been made to develop classifications and algorithms in order to standardize the diagnosis of pain in PD, and numerous studies have addressed the question of the pathophysiological mechanisms underlying pain in PD.

1. Clinical description of pain in PD

1.1. Prevalence of pain and pharmacoepidemiology

Painful phenomena are reported in 30 to 85% (mean 66%) of PD patients.(1–5) The discrepancies of prevalence among different studies reflect the absence of clear diagnostic criteria and a poor knowledge of this non-motor symptom by the medical community. Moreover, this variability in the estimation of prevalence is also related to differences in sample sizes, different scales used for the diagnosis of pain depending on the studies, and different types of pain coexisting (5–7). One study aimed to estimate the frequency of pain in PD patients using analgesic prescription histories and to compare it with the general population based on two samples of painful patients (diabetes and osteoarthritis) using a pharmacoepidemiological design (8). Pain estimated by analgesic drug prescription was more prevalent in PD patients than in the general population with an estimated 82% prevalence of pain in PD (versus 76.6% in the general population), and an estimated 33% prevalence of chronic pain in PD, (versus 20% in the general population). Prescriptions of antidepressants and antiepileptic drugs for their analgesic properties were substantially more frequent in PD patients in comparison with the three control populations, suggesting that the prescribing

doctors may have suspected that their PD patients had neuropathic pain because these drugs are the most frequently used drugs for neuropathic pain (8). Thus pain observed in PD appears to be different than pain observed in osteoarthritis, and appears to be related to several subtypes of pain.

1.2. Pain impact on quality of life

Pain is one of the most invalidating non-motor symptoms in Parkinson's disease (PD) with a strong impact on patients' quality of life, sometimes even taking precedence over motor symptoms (1,7). In the general population, chronic pain has shown a clear correlation with severity of depression and reduced quality of life (9,10). In PD as well, pain has been demonstrated to be a major detrimental factor affecting physical and mental health-related quality of life (11,12) and also leading to reduced autonomy (13). A significant relation between pain and depression has been reported in PD, suggesting that pain issues should be taken into consideration when treating PD patients with depression, and reciprocally (14). Yet, pain is an independent predictor of poorer quality of life, independently of its close relationship with depression. Pain has an effect on quality of life, which is greater than motor impairment and comparable to the effect of motor complications (15).

1.3. Risk factors for pain in PD

Female gender, dyskinesia, postural abnormalities, motor complications and depression are the main predictors for development of pain in PD (6,7,16). Autonomic and affective symptoms, have also been associated with an increased risk of pain, while the severity of motor impairment and of cognitive impairment have not been found to have a statistically significant effect on the severity of pain (1). Younger age has been reported as associated with pain in some studies (1), while disease progression was reported as a risk factor for pain in PD

in others (17). Finally, no relationship between pain and age at diagnosis, disease duration, motor examination, or PD stage was observed in several studies (2,16–18). Thus conflicting results are reported regarding the role of PD progression in the emergence of pain, and this could be related to different pain subtypes occurring at different moments in the course of PD. Thus some studies have reported all pain types to be more prevalent in patients with advanced-stage PD than in early stages, whereas only nociceptive arthritic pain was more prevalent in early-stage PD (3). Moreover, some studies suggest that pain could be present very early in the course of PD and could even precede motor symptoms (19,20). Indeed, 16.4% of PD patients have been reported to have presented chronic pain before the diagnosis of PD (21). It is then possible that pain observed at the premotor phase and pain observed late in the disease could have different characteristics leading to discrepant findings among studies. The same heterogeneity could explain the fact that pain in PD is reported to be worse in the OFF state by 17% of participants, whereas 2% describe it as worse in the ON state and 81% report there is no difference between the ON and OFF state with regards to pain severity (1).

1.4. Different pain subtypes

Pain in PD is difficult to describe for patients but also for neurologists, and various features are reported such as muscle cramps, painful dystonia, aching, numbness, and tingling, burning, vibrating, or lancinating pain, reflecting the heterogeneity and complexity of these painful experiences. Ford (1998) defined five subtypes in PD: musculoskeletal, radicular/peripheral neuropathy, dystonic, central pain and akathisia. Yet, different pain subtypes can coexist in a same patient (22). It has thus been found that 29% of PD patients with pain suffered from one type, 35% from two types, 10% from three types of pain, and 2% reported having four concurrent types of pain (3). In the same vein, it has been found that 74–

82% of patients had three or less types of pain (2,6,15). This is a very important finding, because each type of pain requires a different therapeutic approach.

The distinction between these different pain subtypes in Parkinson's patients is still poorly carried out in clinical practice, and their respective prevalence is therefore poorly known and varies from study to study (**Table 1**). Differences may have several explanations, such as the specific focus of the study, different severity stages in the studied PD populations, or methods of classification used. For example, Valkovic et al. reported that musculoskeletal pain (41%) and radicular back pain (27%) were the most prevalent types, and dystonic pain (17%) the least prevalent type (3). Beiske et al. reported 70% prevalence of musculoskeletal, 40% dystonic, and 20% radicular pain in their PD cohort (2). Rana et al. observed that musculoskeletal pain was prevalent only in 28% and dystonic pain, in 48% (4). In contrast, Broetz et al. found up to 36% occurrence of radicular pain (23). Valkovic et al. showed the highest prevalence (22%) for central neuropathic pain (3), in contrast to previous studies (4.5–12.7%) (2,5,24). Moreover, pain severity was highest in central parkinsonian pain followed by dystonic, musculoskeletal, and radicular/peripheral neuropathic pain (21). Central parkinsonian pain is probably underdiagnosed due to its complexity and the lack of clear diagnostic criteria, leading to insufficient recognition and treatment (2,21,25). Indeed, a successful approach to distinguish between these pain subtypes is required so that effective treatment strategies can be established.

1.5. Classifications for pain

The first recognized classification of pain in PD defined five subtypes: musculoskeletal, radicular/peripheral neuropathy, dystonic, central pain and akathisia (**Table 2**) (26). The main limitation of this classification is that it relies on numerous clinical features that may be present, meaning that they also may not be present. Before this classification, pain in PD was

generally classified depending on its relationship to PD: pain “related to PD” or “not related to PD” (6,7). Pain was considered “related to PD” if there was a temporal and/or topographical relationship with PD (onset and location), if pain was influenced by motor complications, or by antiparkinsonian medication, and depending on the patient’s opinion about the relationship between pain and PD. Increasing knowledge regarding the mechanisms of pain led to the emergence of more precise classifications that do not contradict previous approaches, but combine several aspects of previous classifications (22). Wasner and Deuschl proposed a four-tier taxonomy to improve the characterization of the complexity of pain in PD. This taxonomy combines the categorization proposed earlier by Lee et al. or Nègre-Pages et al. depending on the relationship to PD, and assigns nociceptive, neuropathic and miscellaneous pains to distinct categories, as well as further characterization into subcategories. The limitation of this classification is the lack of clarity of miscellaneous subtypes (pain that cannot be clearly assigned as nociceptive or neuropathic). The Marburg-Sao-Paulo-Créteil Questionnaire for Pain in Parkinson's Disease is also an original questionnaire for pain assessment in PD, based on practical clinical reasoning but does not include central pain (17). King's PD Pain Scale (KPPS) includes 14 items rating the severity and frequency of pain, covering seven main domains (27). However different domains are not specific, may be common to different subtypes of pain, thus KPPS is suggested but not recommended for pain classification in PD (28).

Among these different proposed classifications, the definition of parkinsonian central pain (PCP) varies and fails to be precise. Given the lack of reliable validated positive clinical criteria for PCP, and since clinical features of PCP are difficult to specify, it has been recently proposed to standardize PCP diagnosis. Indeed, from the new classification of chronic pain in general population (29), it has been proposed to classify pain in PD into nociceptive, neuropathic and nociplastic pain, either specific or unspecific to PD (**Table 3**) (25). From this

new proposed classification, an algorithm was suggested, aiming to disentangle PCP from other chronic pain subtypes in PD by specifically and sequentially ruling out what is not PCP (25).

A better classification of pain in PD is crucial in order to homogenize the populations in studies aiming to improve our comprehension of pathophysiological mechanisms of pain in PD.

Pathophysiological aspects

Based on the physical pathological approach and according to the International Association for the Study of Pain (IASP), we can define different kinds of pain in PD according to their potential mechanisms (25). Nociceptive pain and neuropathic pain result from a lesion of the somatosensory system and nociplastic pain results from a dysfunction of the somatosensory central system without any evidence of lesion (29). These different kinds of pain can be specific or unspecific to PD. Unspecific pain is related to other painful conditions such as musculoskeletal pain, radicular pain or due to restless leg syndrome. They can be worsened by PD. Specific pain is defined by the presence of chronological and/or topographical links with no evidence of other painful condition. These specific pains can either be nociceptive (directly related to motor symptoms such as the dystonic pain) or nociplastic called central, PCP (25). Abnormal pain processing in PD has been suggested by several studies. For instance, reduced pain thresholds were shown in experimental animal models of PD (30). In addition PD patients also presented decreased subjective and objective pain thresholds to various stimuli in comparison to healthy volunteers (31–33). Recently, two meta-analyses have confirmed the increase in pain perception in PD patients (34,35). Beside pain threshold studies, other arguments in favor of this abnormal pain processing are the abnormalities of laser evoked potentials and the brain modifications induced by pain in PD patients (32,36,37).

In fact, functional imaging using $H_2^{15}O$ -PET scan have shown that, in OFF levodopa condition, pain-free PD patients have overactivation in several nociceptive areas (ipsilateral prefrontal cortex, ipsilateral insula, and contralateral anterior cingulate) in comparison with normal subjects (32). Thus, both sensory discriminative (insula/SII) as well as affective motivational processing of pain (anterior cingulate cortex, prefrontal cortex) are abnormal in PD. In line with these results, it has been reported that both pain threshold (evaluating the sensory-discriminative component of pain) and tolerance thresholds (referring to the psychological perception of pain, a complex balance between cognitive and affective functions) were increased in PD patients after subthalamic nucleus deep brain stimulation and after acute levodopa administration (38,39). Thus, several findings – such as results of imaging studies and the abnormalities found in quantitative sensory assessments as well as laser evoked potentials and nociceptive flexion reflex – suggest that the abnormal pain processing could be located in the central nervous system. But peripheral deafferentation could also play a role in sensory dysfunction (40). However, a recent study using laser evoked potentials, strongly suggests that abnormal nociceptive processing occurs mostly at a central level in PD patients (41). All the previous results indicate that nociceptive signals are amplified somewhere along pain transmission pathways. This could be related to an increased facilitation through a central sensitization of pain pathways (42) or to a decreased inhibition (reduced activity of the descending inhibitory control system) (43,44). An interesting point is the potential existence of a pathophysiological difference between PD patients with persistent pain and pain-free PD patients. Conflicting results have been reported in regard to pain thresholds (lower or similar pain thresholds in painful and pain-free PD patients), so we cannot conclude that the more the patients are painful, the more their pain threshold is lower (36,37). By contrast, functional imaging study comparing pain-induced activation in PD patients with central pain and without any pain

showed a preferential recruitment of the medial affective system in painful patients. Thus the existence of painful sensation might result from an imbalance between the two systems (discriminative and affective) with an overactivation of the medial affective system (31). Other imaging study confirmed these abnormalities using structural and functional magnetic resonance imaging (45). PD patients with persistent pain had significant thinning and functional changes in several nociceptive areas compared to PD patients without pain. All these imaging results suggest the existence of a network of brain regional alterations specifically associated with pain. These brain modifications are not related to chronic dopaminergic treatment because de novo PD patients never treated by dopaminergic drugs showed overactivations in several nociceptive areas at functional magnetic resonance imaging with experimental pain stimulation (46). Finally, the role of the dopaminergic system in the pathophysiology of pain remains an open question. Most studies have reported that L-Dopa reduces pain perception. For instance, L- Dopa raised subjective cold pain thresholds, decreased pain intensity and reduced cerebral overactivations induced by experimental pain stimulation (32,33,36,47). Nevertheless, a dopamine agonist (apomorphine) did not modify pain threshold or cerebral activations induced by pain stimulation (48). Moreover, in an imaging correlation study, subjective pain threshold was not correlated with FP-CIT binding ratio in striatum and but there was a significant correlation with FP-CIT binding ratio in extrastriatal regions (posterior cingulate cortex and insula) suggesting that pain perception abnormalities may be related to other monoaminergic systems (49). The same hypothesis was proposed in animal models. Norepinephrine and serotonin reuptake inhibitors decreased or prevented hypersensitivity in six OHDA rats (50,51). In addition, these drugs normalized spinal enkephalin immunoreactivity in the spinal cord in these rats. Thus, hyperalgesia in the rat model of PD is not mediated by nigral dopaminergic lesion alone but by other monoaminergic systems (norepinephrine and serotonin) which modulate the opioid system.

To conclude, several neurotransmitters such as dopamine, norepinephrine, serotonin and opioid could participate in the abnormal pain processing in PD.

Conclusion

Numerous clinical and preclinical studies show that PD should now be considered as a painful disease, at least, as much as osteoarthritis and diabetes. Yet, the coexistence of different pain subtypes in PD requires a successful approach to distinguish between these pains so that effective treatment strategies can be established. In particular, the identification of parkinsonian central pain remains uneasy and clear positive diagnosis criteria still need to be validated. More, generally, a better classification of pain in PD and better homogenization of populations is of major importance for further studies aiming to improve our comprehension of pathophysiological mechanisms of pain in PD.

Abbreviations: PD: parkinson's disease; PCP: Parkinsonian central pain.

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TABLES

Table 1: Prevalence of pain subtypes according to different studies conducted in PD

	Muskulo- skeletal	Dystonic	Radicular- Neuropathic	Central	Others
<i>Broetz et al 2007</i>	74.3%		35.6%		
<i>Defazio et al 2008</i>	25.4%	11.4%	4.7%	4.5%	
<i>Beiske et al 2009</i>	70%	40%	20%	10%	
<i>Rana et al 2013</i>	48%	26%	13%	8%	
<i>Valkovic et al 2015</i>					
Early stage	34%	11%	19%	19%	26%
Advanced stage	47%	23%	34%	25%	23%
<i>Silverdale et al 2018</i>	66%	16%	34%	27%	

Table 2: Clinical classification of painful or unpleasant sensations in PD according to Ford et al.

Category by description	Clinical features
Musculoskeletal	<ul style="list-style-type: none"> • Aching, cramping, arthralgic, myalgic sensations in joints, and muscles • Associated findings may include tenderness, arthritic changes, skeletal deformity, limited joint mobility, postural abnormalities, and arthralgic gait; • May be exacerbated by parkinsonian rigidity, stiffness and immobility, and relieved by mobility; • May fluctuate with medication dosing and improve with levodopa
Radicular/neuropathic	<ul style="list-style-type: none"> • Pain in a root or nerve territory, associated with motor or sensory signs of nerve or root entrapment
Dystonia	<ul style="list-style-type: none"> • Associated with 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, beginning of dose and end of dose dystonia, peak dose dystonia
Central primary pain	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Subjective sense of relentness, often accompanied by an urge to move; • May fluctuate with medication effect, and improve with levodopa

Table 3: Clinical classification of painful or unpleasant sensations in PD according to Marques et al.

<i>Chronic pain</i>	<i>Nociceptive pain</i>	<i>Neuropathic pain</i>	<i>Nociplastic pain</i>
<i>Unspecific to PD</i>	<i>Musculoskeletal pain</i>	<i>Radicular pain</i>	<i>RLS</i>
<i>Specific in PD</i>	<i>Dystonic pain</i>	-	<i>Central Pain</i>