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Review

Pain in Parkinson's Disease: Pathophysiology, Classification and Treatment

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Abstract

Continuous medical progress is significantly improving the quality of health care. As a result, people are living longer than during the past century, but this has also caused an increase of the prevalence of many neurological disorders. Parkinson's disease (PD) is the fastest growing neurological condition, with a doubling of cases reported between 1995 and 2015 and a further doubling projected by 2030. Parkinson's disease is generally associated with characteristic motor symptoms (resting tremor, rigidity, bradykinesia and postural instability). However, patients with PD also experience many non-motor symptoms that might be at least as debilitating as the motor symptoms and which significantly impact patients' quality of life (QoL). Pain is a frequent yet underrecognized symptom; the incidence in PD is much higher than in the general population and constitutes a silent disability that significantly contributes to a deterioration in QoL. Accurate identification of parkinsonian pain is important for its diagnosis and effective treatment. In this review, we provide an overview of the pathophysiology, classification, and management of pain in PD. We define the various modalities of chronic PD pain, suggesting possible explanations for its relationship with PD pathology, and discuss its management and currently recommended therapies.

Keywords: Parkinson's disease; pain; therapy; non-motor symptoms

1. Introduction

James Parkinson described the comorbidity of pain in Parkinson's disease (PD) in his original 1817 paper [1]. Pain is one of the most frequently reported non-motor symptoms by patients with Parkinson's disease, with a prevalence of 40–85% [2]. However, it is often underestimated and undertreated, despite having a significant impact on patients' quality of life (QoL). About 50% of PD patients with pain do not receive any analgesic treatment [3]. Based on the increasing prevalence of PD, it is estimated that by 2030 there will be 3.7 million patients with pain worldwide that will remain untreated [4]. Pain is also one of the earliest symptoms of PD, sometimes present at the preclinical stage, and is prominent on the side of the body that was initially or more severely affected by the motor impairment. The neurobiology of pain in PD is complex: The basal ganglia are involved in the processing of nociceptive inputs; thus, nigrostriatal damage may partly account for the sensation of pain experienced in PD. In addition to the dopaminergic systems, other neurotransmission pathways are implicated, such as the serotonergic, noradrenergic, glutamatergic, and GABAergic pathways [5–8]. Knowledge of the mechanisms of transmission and interpretation of pain, assessed by tactile, nociceptive and tolerance thresholds, is therefore essential for adequate therapeutic management [9,10].

2. Pathophysiology

The etiology of pain in PD is multifactorial and complex. In addition to the modification of the basal ganglia activation patterns, the serotonergic raphe nuclei and the noradrenergic locus coeruleus have a role in pain control and are impacted over the course of the illness [11]. Dopamine is known to be involved in pain modulation, influencing both the propagation of noxious stimuli and its perception; changes in dopaminergic function may also modulate sensory perception. For instance, pain occurs more frequently in patients during 'OFF' periods, and pain thresholds are raised by dopaminergic medication [12]. Dopamine is not the only neurotransmitter to be altered in PD. Loss of nigral dopaminergic neurons and the subsequent striatal depletion of dopamine leads to glutamate hyperactivity in the basal ganglia. Peripheral sensory information and pain signals are transmitted to the spinal cord via primary afferent neurons, the majority of which are glutamatergic [13]. Glutamate has also been implicated in the phenomenon underlying chronic pain, including the effects of allodynia and hyperalgesia [14].

Of particular interest is the degeneration of the cholinergic system in PD, that is often more severe than in Alzheimer's disease [15,16]. Acetylcholine acts as neurotransmitter and neuromodulator in both the central and peripheral nervous system [17] and can modify the perception of pain, regulating nociceptive signals via pre- and

post-synaptic mechanisms and involving nicotinic and muscarinic receptors [18]. The primary somatosensory cortex, insular cortex, anterior cingulate cortex, medial prefrontal cortex, and descending modulatory systems are all influenced by cholinergic modulation [18]. The same neurotransmitters are also involved in other PD conditions that can affect pain. Anxiety disorders, for example, can lead to maladaptive pain. Depression, like anxiety, is also frequent in PD and the perception of pain may be altered by a reduction in mood, resulting in higher sensitivity [19].

Patients with PD are often advanced in age. Disease progression over time is associated with biomolecular and cellular alterations in the anatomical regions involved in the experience of pain. Another factor influencing pain perception is sex. Several studies have observed a higher prevalence in females for most of the various syndromes involving pain, including PD [20]. Moreover, pain seems to be associated with the duration and severity of the disease, as well as the presence of motor complications induced by levodopa treatment [21].

3. Pain Assessment in PD

Pain in patients with PD is evaluated in clinical practice using questionnaires. The King's Parkinson's Disease Pain Scale [22] is the only questionnaire totally dedicated to pain. Other scales include the Parkinson's Disease Questionnaire [23] and the MDS-Unified Parkinson's Disease Rating Scale [24]. Other questionnaires investigate aspects of daily life that can affect pain, including the Parkinson's Disease Sleep Scale-2 [25], Fatigue Severity Scale [26], Hamilton Rating Scale for Anxiety [27], and Hamilton Depression Rating Scale [28].

In addition to these questionnaires, there are also neurophysiological assessment tools, such as electrical or thermal stimuli and electrical stimulation combined with electromyography, for evaluating activation of the flexor reflex [29]. Evoked potentials from nociceptive stimulation with lasers (LEPs, laser-evoked potentials) can also be used [30]. Regardless of the different methods, the data agree on reduced pain thresholds and pain tolerance in subjects with PD compared with healthy subjects [31].

4. Pain Classification and Treatment

Classifying pain in PD is not an easy task and there is currently no consensus within the scientific community. Various methods of classifying pain in PD exist. One of the most used in clinical practice is that of Wasner and Deuschl, who proposed the classification of pain in PD at four levels, by combining characteristics of previous classifications and the principles underlying the categorization of chronic pain [32]. The first level of this classification divides pain into PD-related and non-PD-related (tier 1: relationship to PD) [33]. In the second level, the previous two types of pain are classified as nociceptive or neuropathic [4–34]; if it is not clear which of the two categories should be chosen, pain is included in the "miscellaneous" category (tier 2: broad system) [35]. In the third level, the various types of pain are classified according to the categories: musculoskeletal, visceral, cutaneous, peripheral, or central (tier 3: broad type) [36]. In the last (fourth) level, different aspects from a clinical, pathogenetic, and therapeutic point of view are specified (tier 4: specific structures and pathology) [32]. Another important classification method that is frequently used is that of Ford, which considers five categories: musculoskeletal, dystonic, neuropathic/radicular, central/primary, and akathisia [35–37].

4.1 Musculoskeletal Pain

Musculoskeletal pain is the type most frequently complained of by PD patients and generally stems from cramps and aches in muscles or joints, due to postural patterns (camptocormia or Pisa syndrome), gait disturbances, or rigidity and akinesia [38]. The region most involved is the spine, followed by the neck, ankles, hips, and shoulder; the last is important because one of the initial symptoms of the disease is "frozen shoulder" [39].

The treatment of musculoskeletal pain depends on the cause. If it is due to stiffness and/or akinesia, the use of levodopa alongside psychokinesis therapy (PKT) and exercise is suggested [37]. Recently, safinamide (an monoamine oxidase type B (MAO-B) inhibitor and glutamate modulator) has been shown to improve musculoskeletal pain in PD patients [40–43]. In some cases, deep brain stimulation (DBS) is effective in reducing these motor symptoms and thus also the resulting pain [2]. If there are postural changes or deformities, non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics, associated obviously with a suitable PKT, are preferred [11]. In some cases, intra-articular corticosteroid injections or surgery may be required to treat important muscle contractures or to correct deformities [44].

4.2 Dystonic Pain

Dystonia is an uncontrolled and violent muscle contraction that leads to deformities and abnormal postures, and may be one of the most painful symptoms a patient can experience. In some cases, dystonia can lead to dislocations of the shoulder [45]. These dystonic muscle spasms involve various body regions, including the extremities (hands and feet) and the face [46]. They can appear spontaneously or be associated with movements [47]. Dystonia is a complication of dopaminergic treatment and typically arises in the OFF periods, some hours after the intake of the last dose of levodopa, but can present also as peak dose dystonia or dystonic dyskinesia [48]. Levodopa itself seems to be implicated in the pathogenesis of these disorders, as they are practically absent in untreated patients, but appear often after the levodopa "honeymoon" [49]. One hypothesis is that the phenomenon of synaptic plasticity and dysregulation of neurotransmission, possibly associated with acetylcholine, are involved [50].

When dystonia occurs during OFF periods, the first strategy to manage pain is to adjust the levodopa therapy, in order to reduce the wearing-off intervals [51]. Sometimes it is necessary to introduce the administration of apomorphine [52]. Surgical therapy with placement of DBS at the level of the subthalamic nucleus and internal globus pallidus is also of benefit [53]. Finally, botulinum toxin may be useful in localized dystonia [54]. Peak dose dystonia requires, on the contrary, a reduction of the dopaminergic dose, while dystonic dyskinesia may respond to amantadine [55].

4.3 Peripheral and Radicular Neuropathic Pain

In this case, the pain, which can also be associated with paresthesia (manifested with tingling) and numbness, follows the innervation territory of a peripheral nerve or a nerve root [56]. While radicular pain is attributed to postural deformities (frequent in this pathology) and to chronic sequelae of limb immobility due to using a wheelchair [57], peripheral neuropathic pain is not completely understood. Two hypotheses are a vitamin B12 deficiency (serum concentrations decrease in a time-dependent manner with levodopa intake) and the accumulation of neurotoxic substances such as homocysteine or methylmalonic acid [58]. Treatment is similar to that of neuropathic pain in general, although there are few data available in the literature on the efficacy of these lines of therapies, and it should be noted that some drugs can interfere with the cognitive-behavioral profile of the patient [44]. First-line drugs are represented by tricyclic antidepressants (TCAs), antiepileptics (such as pregabalin and gabapentin), and serotonin and norepinephrine reuptake inhibitors (such as duloxetine). Safinamide may also be effective for radicular pain [40–43]. Weak opiates (tramadol or tapentadol) are considered as second-line drugs, while lidocaine or capsaicin in patches are recommended only in peripheral neuropathies [59]. As a third pharmacological line, strong opiates (such as morphine) or injections of botulinum toxin, if the neuropathy is peripheral, are used [60]. In refractory patients, other therapeutic protocols, such as psychotherapy (in particular, cognitive-behavioral), physical therapies (massage, ultrasound), and interventional therapies (neurostimulation, intrathecal and epidural injection, peripheral nerve block) are available [61].

4.4 Central Pain

Central pain is one of the most difficult sensations to describe. Heat, burning, pins and needles, or even piercing (“like a stab wound”) are the reported symptoms, which can also occur in combination [4]. Pain locations can differ. Often, the limb most affected by the disease is involved; however, pain is also felt in the mouth, chest, and abdomen, as well as in the vaginal or testicular area [46]. The cause is not well understood, but it may possibly be due to a processing dysfunction in the affective-emotional component of pain [39]. Although this is not due to dystonia or rigidity, it tends to coincide with motor fluctuations, being more prominent during OFF periods, and may be a consequence of dysfunction in dopaminergic autonomic centers [31]. Therapy is complex, and dopaminergic agents are not particularly effective in relieving this type of pain [62]. Conventional analgesics such as opioids, TCAs, and clozapine are therefore generally used [61]. One additional resource would be the use of cannabinoids, as many receptors for these molecules are present [44] in the regions of the globus pallidus which are involved more often in pain. Finally, some patients have reported benefits with bilateral subthalamic DBS [2].

4.5 Akathisia

Akathisia is a disorder characterized by an inner restlessness and persistent urge or impulse to move or change position [37]. Moreso than pain, it is therefore a very disabling discomfort and can severely limit daily activities such as driving, eating, and socializing [63]. It is very similar to, but must be distinguished from, other conditions, such as anxiety-related urges to move, dyskinesia, somatic urges, such as urinary incontinence, and restless legs syndrome, which is often non-generalized and occurs more frequently during the night [64]. Akathisia is pathogenically related to a dopaminergic deficiency of the mesocortical pathway, which originates from the ventral tegmental area [63]. Indeed, it worsens during OFF states while improving after “adjustment” of dopaminergic therapy [65]. Clozapine, which preferentially affects the mesocortical and mesolimbic dopaminergic systems, may also be helpful [64].

4.6 Non-Pharmacological Management

To improve management of PD pain, a multidisciplinary approach including non-pharmacological treatments is required. Among these, physical exercise, yoga, and tai-chi or qigong have been shown to improve leg strength, balance, and gait, and consequently musculoskeletal pain [66]. When the response to conventional approaches is suboptimal, complementary methods include acupuncture, osteopathy, and massage, which have been shown to effectively reduce stiffness and pain [67]. As previously described, a significant reduction of musculoskeletal and dystonic pain has been shown with DBS [2]. Repetitive transcranial magnetic stimulation is a promising modality for dystonic pain, probably resulting from modulation of the activity in pain-processing areas of the thalamus, insular cortex, and anterior cingulate cortex [68].

5. Conclusions

Pain is an important non-motor PD symptom that has a substantial impact on patients’ QoL and is often overlooked by clinicians. The reasons behind the manifestation of such a vast spectrum of PD pain syndromes are multiple, complex and still not completely understood. Among the

various factors, undoubtedly the motor symptoms (rigidity, postural alterations, motor fluctuations, etc.) contribute to musculoskeletal, dystonic, and neuropathic pain, but the non-motor symptoms, such as dysautonomia, sleep disturbances, and mood disorders, play a role. Classifying pain is useful for choosing the appropriate management options. The treatment of pain is complex and involves various pharmacological, surgical, and rehabilitative approaches. In many cases, pain symptoms are best managed in a multidisciplinary context. The early identification and timely treatment of PD pain may have positive effects on the illness burden, mitigate disability, and improve the QoL of this particularly vulnerable population. Despite several publications describing evolution of chronic PD pain, there is no general consensus within the scientific community regarding its classification and management. This review could be a useful tool for reaching a homogeneous definition of the physiology, clinical manifestations, and treatment strategies for this, often under-estimated and under-treated, important symptom.

Author Contributions

CC and WHJ designed the research study, collected, analyzed literatures; make figures and contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest. Carlo Cattaneo is an employee at Zambon SpA. Wolfgang H. Jost is a member of the Scientific Advisory Board of Zambon SpA. Wolfgang H. Jost is serving as one of the Guest editors of this journal. Wolfgang H. Jost had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

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