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REVIEW ARTICLE

Pain in early-stage Parkinson's disease: Implications from clinical features to pathophysiology mechanisms



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Pain is a common non-motor symptom of Parkinson's disease (PD) that markedly impacts patients' quality of life. Although pain occurs mostly secondary to motor disability of PD, pain may antedate motor symptoms by years. Numerous studies have shown that PD patients manifest altered sensory and pain thresholds compared with control subjects. Although both levodopa and deep brain stimulation improve motor symptoms, there remains no direct correlation between motor improvement and altered pain sensitivity, suggesting that motor symptoms and pain do not necessarily share pathogenetic mechanisms. Whether nociceptive processing is dysfunctional in the early stages of PD, when motor symptoms are not prominent, remains uncertain. In this review, we highlight the evidence for disrupted nociceptive processing in patients with early-stage PD. Painful symptoms and aberrant pain processing in early PD are associated with both central and peripheral deafferentation. Dopamine depletion in selective striatal regions, and the development of Lewy pathology in specific non-dopaminergic subcortical areas, underlie the clinical features of pain at this early disease stage. An increased awareness of pain as an early feature of PD might provide further insights into a mechanism-based approach to sensory system dysregulation in this disease.

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¹ Both authors declare that there is no conflict of interest regarding the publication of this paper.

Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder that imposes a considerable, and mounting, economic burden for those societies with increasingly aged populations.¹ Disability in patients with PD is primarily due to their impaired motor function presented as resting tremor, rigidity, bradykinesia and posture instability. However, sensory symptoms, especially pain, are frequent complaints during the course of the illness,² and affect more than two-thirds of patients.^{3–5} Although pain is mostly secondary to motor disability (e.g. musculoskeletal or dystonic pain), as many as 43% of PD patients experience "primary pain" in the early stages of PD, when motor symptoms are not yet prominent.⁶ In addition, symptoms of pain may antedate the onset of classic parkinsonism motor features by years.^{7,8} In our previous nationwide prospective cohort study, patients with pain symptoms had an increased risk of PD compared with patients who were pain-free, with a dose–response relationship between pain severity and the incidence of PD.⁸ These findings suggest that pain at an early or premotor stage of PD raise the possibility of sensory system dysfunction in either the peripheral or central compartments of the nociceptive pathways during the early course of the disease.

As pain is a common pre-motor feature of PD, its early identification in susceptible subjects may facilitate early disease detection and appropriate management during the early course of the disease. To this end, a thorough understanding of the relevant clinical manifestations and potential pathogenic mechanisms of pain during the early period of PD are required. Several studies have explored the prevalence and characteristics of pain in patients with PD but with inconsistent results. However, evaluating and separating PD-related pain from pain of other origins is an important challenge. In patients with advanced stage of PD, pain may come from the common aging related orthopedic comorbidities, such as osteoarthritis and lumbar-sacral radiculopathy (Figure 1), and these non-PD pain causes contribute to the heterogeneous results of previous studies. To avoid the complexity of mixed origins of pain in patients with advanced PD, the current review summarizes the clinical features of pain processing following receipt of a painful stimulus, and the relationships between pain and motor manifestations in patients with early-stage PD. Given that our focus is on early-stage PD, we have restricted our review to patients at the early stages of this disease (Hoehn and Yahr (H–Y) stage < 3), including drug-naïve patients.

Clinical features of pain in early-stage PD

In early-stage PD, pain was rated as one of the most bothersome non-motor symptoms.⁹ Although many studies have shown complaints of shoulder pain might precede a diagnosis of PD for several months or years before the first motor symptoms develop.^{10–12} However, a direct link between PD and preceding pain is not available yet and prospective follow-up studies are needed for clarification. Pain and its relationship with the onset of motor symptoms, as well as the presence of other pain etiologies, led to the categories of musculoskeletal pain, neuropathic pain,

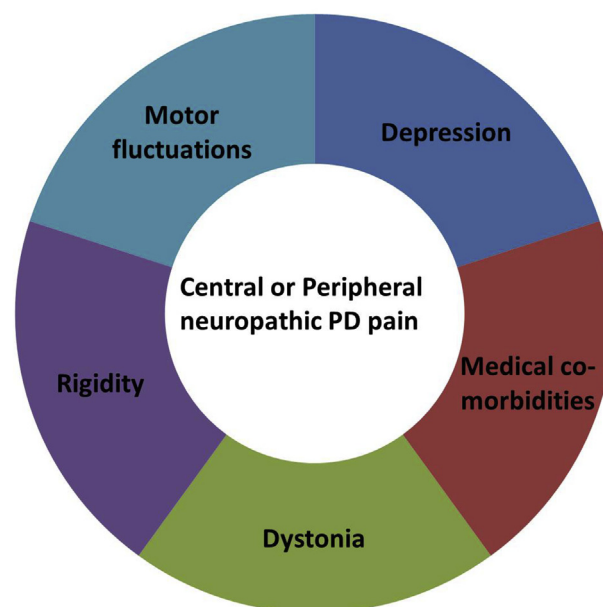


Figure 1 Factors that could lead to pain in patients with PD.

dystonic pain, primary central pain, akathitic discomfort, restless leg syndrome, other co-morbidities related pain (Figure 1).¹³ The most frequently occurring pain types in PD are musculoskeletal and dystonic pain, affecting 70% and 40% of patients, respectively.³ Pain in distinct locations, particularly the shoulders or hips, commonly predates a diagnosis of PD by months or even years.^{10,14,15} In a population-based study, pain and abnormal sensations were more frequent in patients with the postural instability and gait difficulty motor-subtype than in those with the tremor-dominant subtype.⁵

The relationships between pain and the cardinal motor symptoms of PD during the early-stages of disease remain obscure. Some studies indicate that pain symptoms in early and drug-naïve PD patients are associated with the severity of motor disability. The location of pain usually corresponds to the body part most severely affected by the illness. Further, patients with a higher score on the H–Y stage were associated with more complaints of pain.⁵ In patients with pain as the presenting symptom, anti-parkinsonian treatment relieves not only motor symptoms, but also the pain itself.¹⁶ These observations imply that pain in early PD is a co-morbidity of the presenting motor symptoms. However, contradictory findings have been reported. The appearance of pain may precede the onset of motor features of parkinsonism by several years.¹⁷ Subsequent studies have shown that pain symptoms could be independently associated with the risk and incidence of PD.^{7,8} However, a survey of shoulder pain in a cohort of early PD patients (mean H–Y stage of 2.2) revealed no association between pain and H–Y stages, with pain occurring in both the affected and unaffected side.¹⁰ Studies comparing early PD patients with primary central pain versus those without pain also failed to reveal significant differences in motor severity.^{18,19} These observations suggest that pain is not simply a comorbidity of motor disability in early stages of the disease.

Previous studies have shown that dopamine can modulate nociceptive processing in different central nociceptive

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