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Pain in Parkinson's Disease

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Abstract: Parkinson's disease is characterized primarily as a neurodegenerative disorder that leads to disabling motor and cognitive impairment. PD is less widely appreciated as a disease causing a substantial variety of pain syndromes, although the prevalence of pain in PD is approximately 40%. In a minority of patients, pain is so severe and intractable that it overshadows the motor symptoms of the disorder. In recent years, descriptive surveys of non-motor symptoms in PD have led to a classification of painful sensations into one or more of several categories: musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, akathitic discomfort, and primary, central parkinsonian pain. A framework for diagnosing and treating painful PD is described in this review, together with recent insignts into the neurophysiological mechanisms and substrates of pain in PD. © 2010 Movement Disorder Society

Key words: pain; Parkinson's disease; dystonia; non-motor fluctuations

Pain is an important and distressing symptom in Parkinson's disease (PD). A frequently overlooked clinical feature of PD, pain may be severe enough to overshadow the motor symptoms of the disorder. James Parkinson wrote in his famous monograph that painful symptoms can be the first sign of impairment[1] and detailed descriptions of painful sensations are found in every early report of the disease.[1–6] In the modern era, several surveys of painful symptoms in PD have led to a clinical framework for the evaluation and treatment of Parkinson pain.[7–12] At the same time, there has emerged an increasing understanding of the sensory functions of the basal ganglia and the electrophysiology of sensory processing in patients with PD.[13,14]

About 40% of patients with PD experience substantial pain or unpleasant sensations.[10] For diagnostic purposes, it is helpful to classify pain in PD into one or more of five categories: musculoskeletal pain, radicular, or neuropathic pain, dystonia-related pain, akathitic discomfort, and primary, or central, parkinsonian pain (Table 1). The most prevalent painful sensations are caused by muscle cramping or dystonia.[9]

NEUROANATOMICAL AND NEUROPHYSIOLOGICAL CONSIDERATIONS

The neuroanatomical pathways that mediate pain perception in Parkinson disease are arranged in two distinct systems (Fig. 1): the lateral pain pathway, comprising the spinothalamic tract, is a fast conducting system that projects directly to the thalamus and primary sensory cortex, subserving the discriminatory elements of pain.[15] The medial spinoreticulothalamic pathway is a system of slow conducting fibers that projects to the medullary core and mesencephalon, with synapses in the nucleus gigantocellularis, parabrachial region, periaqueductal grey and hypothalamus, intralaminar and medial thalamic nuclei, as well as the insula, parietal operculum, anterior cingulate cortex, amygdala, and hippocampus.[15] This pain pathway has intimate association with the autonomic nervous system, and appears to subserve the autonomic, affective, and cognitive dimensions of pain.[15] Within the medial pain pathway, several structures are the site of neuronal loss and Lewy bodies, including the parabrachial nucleus locus coeruleus and periaqueductal grey.

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TABLE 1. *Clinical classification of painful or unpleasant sensations in Parkinson's disease*

Category by description	Clinical features	Clinical approach
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	Routine musculoskeletal evaluation, with rheumatological or orthopedic consultation; Physical and occupational therapy, passive or active range of motion exercises, prevention of contractures, analgesia and anti-inflammatory agents, and orthopedic joint surgery as indicated, with subsequent rehabilitation
Radicular/neuropathic	Pain in a root or nerve territory, associated with motor or sensory signs of nerve or root entrapment	Routine neurological and electrodiagnostic work-up; Avoidance of overuse or poor posture, physical and occupational therapy, decompressive surgery as indicated
Dystonia	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	Attempt to optimize dopaminergic treatment to reduce "off" fluctuations or medication-induced dystonia; Anticholinergics, amantadine, baclofen, apomorphine, injections of botulinum toxin; Subthalamic nucleus or globus pallidus interna stimulation
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	Levodopa and dopaminergic agents may help; Neuropathic pain agents, such as carbamazepine, gabapentin, tricyclic antidepressants, and opiates
Akathisia	Subjective sense of restlessness, often accompanied by an urge to move; May fluctuate with medication effect, and improve with levodopa	Levodopa, dopamine agonists, opiates

The neurophysiology of pain perception in PD is not well understood. There is abundant indirect evidence of abnormal somatoensory processing with the basal ganglia that involves the substantia nigra, caudate, putamen, globus pallidus, thalamus, and their interconnections.[13] It has been proposed that the basal ganglia perform an important gating role for nociceptive information within the striatum and limbic system before it reaches consciousness.[16,17] Although nerve conduction along peripheral and central pathways appears to be normal, there is abnormal nociceptive processing and pain-induced abnormalities in autonomic function.[18] Dopamine appears to modulate the experience of pain perception by increasing the pain threshold,[19,20] and the absence of levodopa (L-dopa) in PD patients results in widespread activation of sensory cortex in response to pain.[21]

CLINICAL APPROACH TO PAIN SYNDROMES IN PD

As a general approach, painful symptoms in PD should be considered in relation to the cardinal symptoms of tremor, rigidity, akinesia, dystonia, and akathisia that occur in PD. It is important to note whether antiparkinsonian medications induce, exacerbate or relieve PD-associated pain. Pain caused by dystonia can be diagnosed when there is visible twisting, cramping, posturing of the painful extremity or body part. Akathisia, while not painful is intensely unpleasant, and represents a distinctive symptom that occurs in PD. Primary parkinsonian pain, unrelated to a disturbance in motor function, is presumed to be of central origin, and may be inferred partly by its clinical features, and partly through exclusion of other causes.

Painful symptoms tend to worsen in PD patients who are off medication. For many individuals, however, pain sensations occur in strict relation to the motor fluctuations of the disease, and are designated nonmotor fluctuations.[22,23] Non-motor fluctuations comprise affective and cognitive symptoms, autonomic disturbances, and painful sensations that often have a visceral character, such as abdominal bloating or chest wall tightening. Nonmotor painful sensations may well have an autonomic origin in some patients.

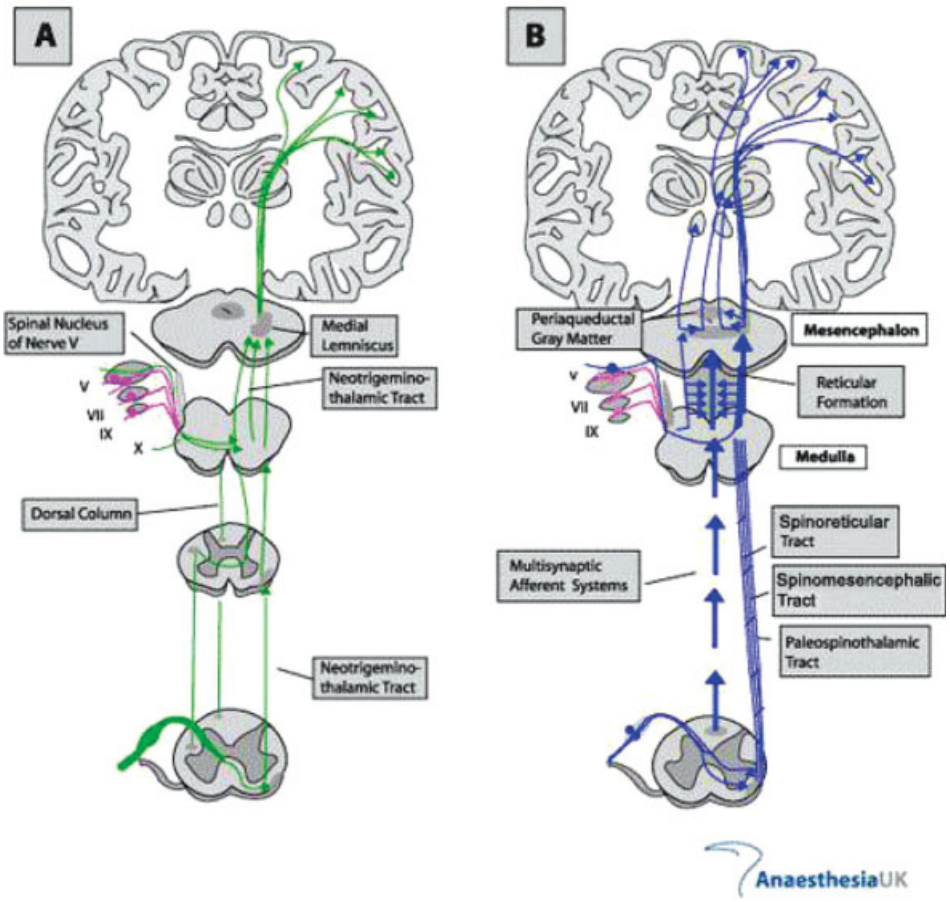

FIG. 1. Central pain pathways in Parkinson's disease [please re-draw].[15] A: Lateral pain pathways, comprising the spinothalamic and neotrigeminothalamic tracts, are fast conducting direct projections to the thalamus and primary sensory cortex, and subserve the discriminatory elements of pain. B: The medial spinoreticulothalamic pathway is a system of slow conducting fibers that projects to the medullary core and mesencephalon, with synapses in the nucleus gigantocellularis, parabrachial region, periaqueductal grey and hypothalamus, intralaminar and medial thalamic nuclei, as well as the insula, parietal operculum, anterior cingulated cortex, amygdale, and hippocampus. The medial pain pathways subserve the affective, autonomic, and cognitive experience of pain. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Musculoskeletal Pain in PD

Pain of musculoskeletal origin has long been described in PD, and, in some studies, appears related to the presence of parkinsonian rigidity and akinesia. The aching, cramping, and joint pains in patients with PD are commonly held to result from a lack of mobility in affected limbs and joints, deformities of posture, stiffness of limb movements and the awkward mechanics of gait.[24–26] Muscle cramps or tightness in PD typically affect the neck, arm, paraspinal or calf muscles, while joint pains occur most frequently in the shoulder, hips, knees, and ankles.[9] Musculoskeletal pain tends to increase during periods of increased parkinsonism.[9] One of the most common musculoskeletal conditions in PD is the frozen shoulder, which may be a presenting sign of the disorder.[27] Spinal deformities and arthritis are well-described in PD, and the extreme flexion posture of parkinsonism is termed camptocormia.[28]

The treatment of musculoskeletal pain in PD depends on the cause. If the pain is due primarily to parkinsonian rigidity, dopaminergic therapy, physical therapy, and an exercise program are indicated. The goal of treatment is to restore mobility, and an exercise program for most patients is an important way to prevent further musculoskeletal problems. Nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics are helpful for rheumatological and orthopedic conditions, in tandem with physical therapy. Passive range of motion exercises are important to prevent contractures in patients with limited mobility, but once formed, a contracture will generally require surgical intervention.

Radicular and Neuritic Pain

Pain and discomfort that is well localized to the territory of a nerve or nerve root is described as radicular or neuritic pain. Radicular or neuritic pain accounted for 14% of the pain syndromes experienced by patients with PD in one survey.[9] In some reports, the paresthetic 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.

Pain Associated with Dystonia

Dystonia describes a sustained, forceful twisting movement that leads to abnormal postures and deformities. Dystonic spasms are among the most painful symptoms that a patient with PD may experience. The spasms may be paroxysmal, spontaneous, or triggered by movement or activity. They may be brief, lasting minutes, or prolonged, lasting hours, or even be continuous, unrelieved by treatment attempts.[29] By contrast, the classic flowing, writhing, choreathetotic dyskinesias induced by dopaminergic medication are not sustained or painful, and are generally referred to as choreic.

The evaluation of dystonia requires careful consideration of its relationship to dopaminergic medication, and the classification proposed by Quinn provides a helpful clinical framework.[30,31] Dystonia may occur as an early morning manifestation of dopaminergic deficiency, or as a wearing off phenomenon later in the day, or in the middle of the night. Arm dystonia may be severe enough to cause shoulder subluxation, and leg dystonia can produce a dystonic gait. Some patients experience a gradual increase in dystonia over time as their parkinsonism advances, suggesting the possibility of an underlying atypical parkinsonian syndrome, such as striatonigral degeneration.

Early morning dystonia is typically relieved by activity, or shortly after the first dose of dopaminergic medication in the day. In some patients, early morning dystonia is so severe that subcutaneous injections of apomorphine, with its onset of action in minutes, can be justified.[32] When dystonia occurs as a wearing off effect during the day, the treatment is aimed at reducing the duration of the off period. Dopaminergic agents, including long-acting L-dopa, dopamine agonists, or apomorphine, can all be effective.[33] Injections of botulinum toxin may also be helpful to treat focal dystonia in PD.[34,35] Both subthalamic nucleus (STN) stimulation[36] and globus pallidus interna (GPi) stimulation[37] can be effective for treating dystonia in PD. It is noted that deep brain stimulation can also exacerbate dystonia, attributed to inadvertent stimulation of the internal capsule. Intrathecal baclofen, effective for spasticity of spinal or cerebral origin, has shown little effect on the dystonia associated with parkinsonism.[38]

Central Pain Syndromes

Central pain in PD is presumed to be a direct consequence of the disease itself, and not the result of dystonia, rigidity, or a musculoskeletal cause. The concept of primary parkinsonian pain was outlined in the seminal description of Souques in 1921,[4] in which he described bizarre unexplained sensations of stabbing, burning, scalding, formication—all descriptions that have been associated with "neuropathic" pain originating in the central or peripheral nervous system.

There are several reports of unusual pain syndromes involving the face, head, pharynx, epigastrium, abdomen, pelvis, rectum, and genitalia,[7,30,39,40] all areas in which painful dystonia or musculoskeletal conditions are unlikely or implausible. Pain of central origin may have a relentless, obsessional, distressing quality that overshadows the patients' other parkinsonian symptoms.[38] Moreover, in some patients with painful sensations that fluctuate with the medication dosing schedule, the pain may have a distinctly autonomic or visceral character,[41] although internal diagnostic studies reveal no abnormality. The origin of these painful sensations is not understood but it is tempting to speculate that abnormal function of the medial spinoreticulothalamic pathways and their autonomic connections may play a role.

The treatment of presumed central pain in PD is challenging, especially if dopaminergic agents, the first line of therapy for this disabling problem, are not effective. Conventional analgesics, opiates, tricyclics, and atypical neuroleptics, including clozapine, may be helpful.[40] Some individuals have experienced relief of pain after bilateral subthalamic nucleus stimulation.[42] Peripheral nerve blockade does not abolish the pain, supporting the notion that parkinsonian pain originates in the central nervous system.

Akathisia

Restlessness is a frequent and potentially disabling complaint in PD. Parkinsonian akathisia is defined as subjective inner restlessness, producing an intolerance of remaining still, and manifesting as a constant need to move or change position. This complaint has long been observed in PD, and must be distinguished from a need to move due to somatic urges, dyskinesias, anxiety, depression or claustrophobia. The link between

akathisia and a dopaminergic deficit is well established, as the two other major causes of the syndrome are postencephalitic parkinsonism and neuroleptic-induced akathisia. It has been suggested that akathisia results from a dopaminergic deficiency involving the mesocortical pathway, which originates in the ventral tegmental area and is known to be affected in PD.[43]

Parkinsonian akathisia can be severe: patients may be unable to sit, drive a car, eat at a table, or attend social gatherings.[44] In about half of the reported cases of parkinsonian akathisia, the symptom fluctuates with L-dopa dosing schedules,[45] and can be relieved by additional dopaminergic treatment.

SUMMARY

The diverse literature on pain in PD ranges from early clinical descriptions to systematic pain surveys, from speculations regarding the origin of central pain in PD to a growing understanding of the neurophysiological and neuroanatomical substrate of pain in PD. In all series, approximately 40% of patients with PD experience pain, and in a minority of these individuals, the problem is so intractable that it becomes the most distressing symptom of PD. Most parkinsonism-related pain can be assigned to one or more of five categories that allow rational intervention strategies musculoskeletal pain, neuritic or radicular pain, dystonia-associated pain, primary or central pain, and akathitic discomfort. Depression is common in PD and may contribute to the intractability of a chronic pain syndrome. As such, depression needs appropriate recognition and treatment as part of the clinical approach to pain in PD.

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