Global Journal of Medical Research: A
Neurology and Nervous System
Volume 20 Issue 1 Version 1.0 Year 2020
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Pain in Parkinson's Disease: From the Pathogenetic Basics to Treatment Principles

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Abstract- Pain syndromes are quite common in Parkinson's disease, in addition to the motor defect, can significantly worsen the quality of life. Various types of pain related to PD have been described. Different clinical characteristics of the pain, variable relationship with motor symptoms, and variable response to dopaminergic drugs, as well as, in some cases, the dependence its appearance in a specific time of the day, suggest that pain in PD has a complex mechanism with the widespread impairment of the sensory information transmission at different levels of the CNS. In addition to the dopaminergic systems of the brain and spinal cord, non-dopaminergic systems (nor epinephrine, serotonin, gamma-amino butyric acid, glutamate, endorphin, melatonin) are also involved in the development pain syndromes in PD. A neurodegenerative process associated with PD establishes a new dynamic balance between the nociceptive and antinociceptive systems, which ultimately determines the level of pain susceptibility and the pain experience characteristics. Basal ganglia along with amygdala, intralaminar nuclei of the thalamus, insula, prefrontal cortex, anterior and posterior cingulate cortex determine the motor, emotional, autonomic and cognitive responses to pain.

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GJMR-A Classification: NLMC Code: WL 359

Strictly as per the compliance and regulations of:

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I. Introduction

Pain syndromes are quite common in Parkinson's disease (PD), in addition to the motor defect, can significantly worsen the quality of life, being a source of stress and adjustment disorders. The prevalence of chronic pain in patients with PD varies widely from 34% to 83%, which is due to different diagnostic criteria and patient examination methodologies [1, 2, 3]. In some cases, the painful is not so pronounced, and patients may not report this complaint in routine visits to a physician, so it can only be detected by actively interviewing the patient with focus his attention on the pain sensations, as well as using special questionnaires [4].

Pain phenomena are very diverse in their characteristics and can appear at any stage of PD, changing their character and localization throughout the disease. Sometimes pain syndromes precede the motor manifestation of the disease, arising on the side of a future motor defect [5, 6]. Most pain syndromes fluctuate in parallel with motor symptoms [7] and therefore, are considered non-motor sensory fluctuations. A wide variety of pain syndromes suggests the presence of several pathogenetic mechanisms involved in their formation.

All ongoing studies in the field of pain disorders in patients with PD have two substantial drawbacks: 1) the difficulty in objectifying and quantifying (the presence of pain phenomena often do not correspond to objective changes detected using various neurophysiological research methods); 2) different types of pain disorders can be combined in one patient. Therefore, it is difficult to establish whether they are directly related to PD, whether existing pain syndromes are exacerbated by other diseases, or have a random, independent existence. Moreover, in practice, it is often difficult to identify the etiology or mechanisms of specific pain syndromes associated with PD, especially if they are not accurately identified and poorly localized by patients [8].

Ford's classification uses approaches based on the etiology of pain and its association with motor symptoms [9]. Painful symptoms in PD can be classified into five categories: musculoskeletal pain, radicular or neuropathic pain, dystonia-related pain, primary (central) pain, and akathisia.

II. Musculoskeletal Pain

Musculoskeletal pain is most common in patients with PD and is associated with rigidity, akinesia, postural, and tonic defects, which leads to or aggravates existing mobility disorders in the spine and limbs. This type of pain is often localized on the side of a motor defect and is characterized by the presence of myofascial trigger points, tonic tension, and muscle soreness. Changes in muscle tone and postural disorders lead to local overloads of the tendons, bone, and ligament us apparatus [10, 11]. Emerging pain and muscle cramps in patients with PD are the results of limited mobility in the affected limbs. Muscle tightening and cramps typically affect the neck, arms, and paravertebral muscles, while joint pain mainly affects the shoulders, hips, knees, and elbows.

One of the most common musculoskeletal disorders in patients with PD is shoulder stiffness, which may often be the first sign of PD. The prevalence of the

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"frozen shoulder," also called periarthritis or adhesive capsulitis, is higher in patients with PD than in age-matched subjects without PD [12]. It is indicated that in almost all cases, the initial symptoms of PD developed in the upper limbs ipsilaterally to the side of the «frozen shoulder». Hands and feet can also be deformed under the influence of akinesia and dystonic disorders.

Contractures caused by limited mobility due to the painare another category of musculoskeletal pathology in PD. The risk of contracture is proportional to the duration of immobility and the degree of akinesia. PD patients are more likely than older people in the general population to experience conditions such as mandibular joint pathology, bursitis, arthritis, fasciitis, spinal stenosis, and ankylosing spondylitis [13, 14].

III. Radicular or Neuropathic Pain

Radicular pain in PD is a neuropathic pain that occurs due to the concomitant spinal diseases involving the roots of the spinal cord. A characteristic feature of this disorder is that pain and discomfort are well localized by the territory of the nerve or spinal segment innervation and occurs in 14% of patients with PD [15]. At the same time, unpleasant sensations in the form of cooling, numbness, tingling, etc. can be mistakenly classified as central pain syndrome. Postural deformities and muscular-tonic disorders in PD can also predispose to the development of compression radiculopathy or neuropathy, the clinical manifestations of which tend to increase at the peak of dyskinesia [16].

IV. Dystonic Pain

The prevalence of dystonia-related pain ranges from 8% to 47% [17, 18, 19] in patients with PD experiencing pain. Dystonic pain is associated with motor fluctuations and has a relationship with dopaminergic medication. Dystonic spasms are among the most painful symptoms that a patient with PD may experience [8]. Dystonic pain may be spontaneous or triggered by movement or activity; they may be brief (lasting minutes), prolonged (lasting hours), or even continuous. Dystonia in PD can affect any limb, trunk, neck, face, tongue, jaw, pharynx, and vocal cords, usually developing in sites most severely affected by Parkinsonism. Dystonia may occur as an early morning manifestation of dopaminergic deficiency or as a wearing-off phenomenon later in the day or the middle of the night. In some patients, dystonia is a painful beginning-of-dose or end-of-dose phenomenon; in others, it develops at the peak of response to a dose of dopaminergic medication [8]. The most painful is the "end-of-dose" drug dystonia, which decreases or disappears after the next dose of levodopa is administered. Moreover, dystonic spasms of the "off" period often occur in the legs, while painful spasms of the "on" dystonia are localized in the neck, trunk, and cranial muscles. Early morning dystonia is most often a complication of prolonged administration of levodopa and is observed in patients with a long-term course of the disease [10, 20].

V. Akathisia

Akathisia is defined as a feeling of inner restlessness and an inability to remain still and manifesting as a constant need to move or change position. Akathisia is diagnosed in the presence of both motor and sensory components, but their ratio may be different [21]. The sensory component of akathisia is an unpleasant sensation in the form of anxiety, internal tension, painful sensations (crawling sensations, burning, or tingling), which imperatively prompt the patient to move during which these symptoms noticeably weaken. The motor component of akathisia is often represented by stereotypical movements (swaying of the body, constantly changing posture, kicking from foot to foot, wringing or rubbing hands, etc.). In severe cases, excessive motor activity is practically not amenable to arbitrary control. Due to the need for constant movement, such patients cannot keep up the conversation and do any work.

Akathisia is suggested to result from dopaminergic deficiency involving the mesocortical pathway, which originates in the ventral tegmental area and is known to be affected in PD [8]. An imbalance between dopaminergic and serotonergic/noradrenergic neurotransmitter systems [22, 23] also considered as a basis for akathisia. The development of akathisia is most often observed when taking antipsychotics medication [24], other psychotropic medications, especially Selective Serotonin Reuptake Inhibitors [25], monoamine oxidase inhibitor [26], and tricyclic antidepressants [27] have been associated with akathisia. Also antibiotics [28], calcium channel blockers [29], and even illicit drug use such as amphetamine, methamphetamine, and cocaine [30] can elicit akathisia [31]. In PD, akathisia often occurs spontaneously, but more often, its occurrence is associated with wearing-off phenomenon; that is, fluctuations in the severity of akathisia depend on the concentration of levodopa.

VI. Central Pain

The most complex in its characteristics, mechanisms of development and approaches to treatment is primary or central pain. The prevalence of central pain in patients with PD is 10- 12% [32, 33]. This type of pain can be associated with autonomic manifestations, with visceral sensations. It is typically not restricted to a nerve territory and has been described to affect body areas such as the face, head, pharynx, epigastrium, abdomen, pelvis, rectum, and genitalia [34]. Clinical observations also indicate that the unexplained painful sensation predominately localized

on the more affected side especially in the "OFF" state [35, 36]. This indicates a connection a neurotransmitter disorder (dopaminergic deficiency) in the basal ganglia (BG) with impaired of the central pain modulation processes that can be improved with administration of levodopa [37, 38, 39]. The participation of the BG in the pain perception was proved by experimental and clinical studies, the results of which can be expressed in the following provisions: 1) during pain stimulation, the metabolism and blood flow in BG changes; 2) electrical or pharmacological stimulation of GB causes specific behavior of animals, similar to when they experience pain; 3) pain symptoms often occur after damage to the BG [40].

Even though the occurrence of central pain syndrome in PD is associated with adopaminergic depletion in determined brain structures, there is no correspondence between the degree of motor disorders and the severity of pain. So, for example, in some cases, pain is observed contra laterally to the motor symptoms of the disease. Sometimes the appearance of pain can precede the development of classic motor disorders in a few years [41, 42]. The severity of rigidity, bradykinesia, tremor, and postural instability in patients with pain symptoms in PD does not differ from that in patients without pain disorders. Also there is no correlation between the intensity of pain and tremor or rigidity [43, 44]. Although antiparkinsonian drugs reduce the motor symptoms and pain in PD, in some cases, they can also increase painful sensation.

So, its different clinical characteristics, variable relationship with motor symptoms, and variable response to dopaminergic drugs suggest that pain in PD has a complex mechanism with widespread of sensory disorders at different levels of the CNS. Non-dopaminergic systems (nor epinephrine, serotonin, gamma-aminobutyric acid, glutamate, endorphin) involved in the pathogenesis of various motor complications also make a significant contribution to the formation of central pain syndrome [45, 46].

In general terms, we can say that pain is a complex psychological and neurophysiological phenomenon with neural network in volving the lateral and medial pain systems. The lateral pathway, which includes the spinal thalamic tract, is a rapidly conducting system that projects directly to the lateral thalamus, the primary and sensory soma to sensory areas, the parietal operculum, and the insula cortex. The lateral system is significant for the sensory-discriminative component of pain since it provides information about pain localization and duration [47, 48, 49, 50]. Inhibition of the lateral thalamus reducing localization, one of the sensory discrimination elements of pain. The difficulty that patients have in localizing their pain symptoms supports this hypothesis [51].

The medial pathway is a system of slow-conducting fibers that projects in a caudal and rostral direction to higher centers by terminating in the gigantocellular nucleus, locus coeruleus, nucleus raphe magnus, periaqueductal gray, hypothalamus, intralaminar and medial thalamic nuclei, amygdala, hippocampus, anterior cingular cortex. This path has connections with the an autonomic nervous system and provides an autonomic, affective, cognitive «accompaniment» of pain.

The descending pathways originating in the brain stem and cerebral structures also makes a significant contribution to the integration and modulation of nociceptive information in the dorsal horn. The serotonergic, noradrenergic, and dopaminergic networks are the principal components of these descending pain mechanisms. [48].

Hypothalamic A11- A14 dopaminergic neurons project to the brainstem and all levels of the spinal cord, providing the main source of spinal dopamine. A11 dopaminergic function has been linked to pain modulation [52], spinal loco motor networks [53], and restless legs syndrome [54, 55].Dopamine acted as an excitatory and inhibitory neurotransmitter in the spinal cord to regulate sensory, motor as autonomic functions [56].

Dysfunction of the dopaminergic neurons of the ventral tegmental area (VTA) can play a role in the pathogenesis of central pain disorders. The VTA is the origin of the dopaminergic cell bodies of themesocorticolimbic pathway, which is related to the affective and motivational dimensions of pain perception and allows the ventral tegmental area to communicate with the prefrontal cortex and the anterior cingulate cortex [57]. Lesions of the ventral tegmental area can increase sensitivity to pain, while electrical stimulation of the same area can have an analgesic effect [58].Disorders of the VTA lead to appearance such phenomena as RLS, akathisia of the "off" period, "burning mouth" syndrome, pain phenomena, and «burning» in the genital area, etc. Clozapine, which has a high affinity for the D4 receptors of the mesocortical and mesolimbic dopaminergic systems, may be effective in treating this condition.

Patients with PD have significant pathological changes in the serotonergic system, which has an importantrole in the sensory and emotional properties of pain. So, Conte et al. [59] suggest that in PD patients with pain, the degeneration of noradrenergic and serotoninergic neurons in the locus coeruleus and raphe nuclei can be even more pronounced than in the substantia nigra [60]. It was established that the raphe nuclei have a big impact on the central nervous system. Projections from the raphe nuclei also terminate in the dorsal horn of spinal gray matter where they regulate the release of enkephalins, which inhibit pain sensation. Thus, degeneration of serotonergic neurons within the dorsal and median raphe nuclei detected during

pathological studies can play important role in the occurrence of pain [61, 62].

Locus Coeruleus (LC) undergoes the most pronounced degeneration with a significant decrease in the level of nor epinephrine, which gives projections, mainly inhibitory, to almost all regions of the nervous system, including sensory areas (dorsal horn of the spinal cord, the principal sensory nucleus of the trigeminal nerve, parietal cortex, etc.). The occurrence of spontaneous sensory disturbances, perceived by patients as very unpleasant, poorly localized, and uncertain, is associated with degenerative processes in the LC, as well as functional and anatomical defects in the projections connecting the LC with the different structures of the brain [63]. It is also clear that the LC plays an importantrole in controlling autonomic function with involvement a direct output to sympathetic and parasympathetic preganglionic neurons of the IML of the spinal cord in addition to the projections innervating other autonomic nuclei. Moreover, The LC performs nociceptive modulation within the thalamus [64, 65] and densely innervates the amygdale that has great importance in the development of concomitant autonomic reactions, the cognitive evaluative responses and emotional accompaniment of pain phenomena.[37, 49, 65, 66, 67, 68].

In some pain phenomena and RLS, there is a distinct daily rhythm of their occurrence, which may reflect the involvement of the hypothalamic structures that regulate the diurnal cycles of physiological processes in the body. Although dopamine is a well-known modulator of circadian rhythms in the retina, daily changes in the other dopaminergic systems are also observed [69, 70], in particular in the tuberoinfundibular system. Moreover, it should be noted the important role of the imbalance between dopamine and melatonin in the pathogenesis of RLS and other symptoms of PD with daily and seasonal dependence [71, 72, 73]. It is known that melatonin is a multifunctional hormone, which is determined by the wide representation of its receptors in various brain formations. The highest hormone levels and the density of melatonin receptors (MT1, MT2, and MT3) are in the anterior hypothalamus (preoptic, mediobasal areas), followed by the diencephalon, hippocampus, striatum, and neocortex. Damage to any link in the regulation of hormone synthesis, starting from the retina, leads to a decrease in thenight time secretion of melatonin, as well as the desynchronization of circadian and biological rhythms [71, 74]. It was found that in Parkinson's disease, the night time secretion of melatonin is significantly reduced as the secretory activity of the pineal gland in general. Change in melatonin secretion contributes to the development of various non-motor symptoms of PD, including RLS and various pain disorders. It is known that in experimental animals, pineal melatonin has an analgesic effect due to interaction with opiate receptors. Since opioid peptides act as intermediaries of the analgesic effect of melatonin, a decrease in its modulatory functions leads to disorders of the «fine tuning» of the opioidergic system and contributes to the appearance of pain symptoms [71, 73].Melatonin may also mediate its analgesic activity by interacting with benzodiazepine, muscarinic, nicotinic, serotonergic, and α1 and α2-adrenergic receptors located in the different structures of the brain and also in the dorsal horn of the spinal cord [75]. Also melatonin plays a role in the occurrence of non-motor fluctuations in PD. It was established that central pain disorders and other motor and non-motor symptoms of PD (depression, anxiety) are subject to ON-OFF fluctuations during the day and have an association with melatonin dysregulation in the LC-pineal gland system [76].So, Anti-nociceptive and antiallodynic effects of melatonin can be used effectively in the management of pain, including central pain syndrome, which varies in intensity during the ON-OFF fluctuations.

Periaqueductal gray (PAG) is one of the critical components of a descending pain modulatory network that exerts a dual control, inhibitory or excitatory, on nociceptive transmission in the dorsal horn and trigeminal nucleus. The involvement of the PAG in the neurode generative process may also be considered as one of the key factors of central pain syndrome in PD. Most of these targets of PAG inputs are premotor centers that, in turn, project to sensory, motor, or autonomic nuclei of the brainstem and spinal cord [77]. PAG network also includes the prefrontal and anterior cingulate cortex, hypothalamus, amygdala, dorsolateral pontine reticular formation, rostral ventromedial medulla, and caudal rostral ventromedial medulla [77, 78]. Through connections with these structures, the PAG coordinates specific patterns of cardiovascular, respiratory, motor, and pain modulatory responses [79]. Neuronal activity within the PAG is affected by several neurochemical signals, including opioids, endocannabinoids, and neurotensin [80]. This region has been used as the target for brain-stimulating implants in patients with chronic pain.

The complexity and variety of pain syndromes in PD are often caused by a combination of several pathogenetic mechanisms in their development. Moreover, several additional factors also influence the intensity, prevalence and frequency in occurrence of pain phenomena. It is known that emotional factors can increase or decrease nerve impulses from peripheral nociceptors and thus modify the perception of pain. Fairly well studied is the question of the role of depression in the modulation of pain perception [51, 81]. Symptoms of depression can be observed in PD patients, ranging in intensity from mild to severe [82]. For this reason, depression should also be adequately treated. Another factor that can change the pain

perception, is the state of cognitive functions such as attention.

The ascending pain-conveying pathway salong with descending pathways originating in the brainstem and above-mentioned cerebral structures have a great value in the integration and modulation of nociceptive information in the dorsal horn. Also they have extensive connections with brain areas associated with the cognitive-evaluative and affective motivational components of pain [83]. It is well known that the BG play a central role in the modulation of various functions, being a key component of parallel functional thalamus-cortex-BG loops associated with the motor, limbic and associative systems. In these, the BG are engaged not only in motor control but also in the multiplicity of aspects of the pain syndrome, including the integration of motor, emotional, autonomous, and cognitive responses to pain [37, 84]. Data obtained during neuro physiological and neuro imaging studies indicate involvement of the cerebral structures of the limbic circuitry, including the amygdala and intralaminar nuclei of the thalamus. A study using positron emission tomography found increased activation in the insula, prefrontal cortex, and anterior cingulate cortex during the "off" period [85]. All of these are areas of the limbic system associated with the affective-motivational dimension of pain. Morphological alterations in anterior cingulate cortex and posterior cingulate cortex were shown in Voxel-based morphometry studies in patients with chronic pain [86, 87, 88]. It was established that anterior cingulate cortex is involved in cognition and emotions [89], where as posterior cingulate cortex regulates attention and cognition [90]. Moreover, these brain regions interact with each other during pain experience, that is, cognition of and attention to pain [91].

VII. Conclusions

Thus, pain is one of the most frequent non-motor symptoms affecting PD patients and related to pathologic changes in the anatomical structures involved in nociceptive pain mechanisms. Although certain types of pain syndromes associated with PD were identified, in reality, as a rule, there is a combination of different types and pathogenic mechanisms of pain in each case. Maximum consideration of all these mechanisms brings us closer to choosing the right tactics for treating pain syndrome in PD patients. Great progress has been made in the study of pain syndromes in recent years, but many challenges remain, which forces specialists pay more attention to the fundamental issues of this problem. So, for example, the question: Is a chronic pain syndrome a cause of morphological changes in the considered brain regions, or does PD-dependent neurodegenerative process in the same anatomical structures with the corresponding neurotransmitter imbalance predispose to the appearance of pain at a determined stage of the disease?

The question of a causal-relationship between autonomic dysfunction, emotional and personal characteristics of the individual, the presence of depression and pain perception also remains open. The most complicated problem is also the objectification of pain and an objective assessment of its intensity. Because pain intensity is not simply determined by how much noxious information arises from injured areas of the body - pain is the outcome of neural processing at multiple central nervous system sites in the spinal cord and brainstem, limbic system, hypothalamus, and cortex. Moreover, reflex movements, autonomic reactions, altered attention, behavior features, a sense of unpleasantness are all part of the individual pain experience. In chronic pain sufferers, the fundamental excitability of the circuits responsible for all these components is altered, resulting in changes in neural connectivity and cognitive function about which we understand very little.

A neurodegenerative process associated with PD leads to neurotransmitter imbalance and establishes a new dynamic balance between the nociceptive and antinociceptive systems, which ultimately determines the level of pain susceptibility and the characteristics of the pain experience. Therefore, the treatment of pain syndromes in patients with Parkinson's disease should be based on deep profound fundamental knowledge about this problem and have a multidisciplinary approach.

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