# Chronic pain in Parkinson disease

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## Abstract

The study was aimed to assess the modern trends explaining pathogenesis of chronic pain amongst patients with PD. The information search in the open sources was conducted using databases OVID, PubMed and EMBASE, the depth of search was in time frame after 2010. Content analysis was provided for the most pertinent literature reviews and clinical trials. There were selected 12 sources amongst 89 primary found references.

There were discussed the main domains of pathogenesis of chronic pain in Parkinson disease. The approaches to pain management in PD patients primarily depend on the underlying cause. The presence of chronic pain syndrome should be considered as a reason for assessing the adequacy of antiparkinsonian therapy

**Key words: Parkinson disease; chronic pain; pathogenesis; physiology**

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by damage to the nigrostrial dopaminergic system [1-3]. Its prevalence in the general population is 0.05-0.15% [3], but people older 65 years could have a prevalence up to 2.5%% [1, 2].

The main clinical manifestations of PD are tremor, rigidity, akinesia or bradykinesia, hypokinesia and postural instability. In addition to motor disorders, often patients with PD are registered non-motor symptoms, including autonomic, including hyperhidrosis, orthostatic hypotension, sexual and urinary dysfunction, changes in thermoregulation, cardiovascular

disorders, peripheral edema, mydriasis, sleep disorders, neuropsychiatric symptoms e.g. apathy, fatigue, anhedonia, depression, anxiety, panic attacks, dementia etc [4]. Many patients experience a variety of sensory disturbances, including restless legs syndrome, numbness, paresthesia, visual disturbances, and pain [1, 3, 4]. Among these sensory symptoms, pain is observed in approximately 30-50% of patients with CP; however, some authors indicate a higher frequency of pain registration - up to 85% [4, 5]. Pain can appear at any time during the disease, and in some cases it is present until the diagnosis [6]. There is still no consensus on the classification and mechanisms of algogenesis in PD [8, 9].

The study was aimed to assess the modern trends explaining pathogenesis of chronic pain amongst patients with PD

Methods. The information search in the open sources was conducted using databases OVID, PubMed and EMBASE, the depth of search was in time frame after 2010. Content analysis was provided for the most pertinent literature reviews and clinical trials. There were selected 12 sources amongst 89 primary found references.

Results. PD as a multifocal neurodegenerative progressive disease can affect nociception on several levels, ranging from the transmission of pain from peripheral structures to higher centers that provide perception and interpretation of pain impulses. In patients with CP, the number of free and encapsulated nerve endings (Meissner's body) decreases, which leads to peripheral deafferentation [10]. From the early stages of CP, degenerative changes can occur in the spinal cord. Certain neuronal losses are observed in the posteromarginal nucleus (plate I according to B. Rexed) of the posterior horn of the spinal cord [5].

Braak's concept divided the disease into 6 periods [5, 7]. Changes characteristic of the premotor period begin in the olfactory bulb and gradually move to the lower part of the brainstem (including the medulla oblongata and pons) with the accumulation of Lewy bodies (stages 1 and 2). In subsequent symptomatic periods, pathological changes occur in the midbrain, including the substantia nigra (stage 3), the mesocortex (stage 4) and, finally, the neocortex (stage 5-6) [7]. Nociceptive information cannot be transmitted directly from the spinal cord to higher centers [5], because it is modulated by descending pathways that involve different nuclei of the trunk. Some of these nuclei are affected at the beginning of PD [7]. This 6-period classification can be useful for understanding the changes that occur in the anatomical structure of pain associated with higher centers at different stages of CP.

The International Association for the Study of Pain (IASP) has recently published a fairly thorough analysis of the types of pain in PD with consideration of their probable

pathogenesis [10]. It is known that there are several anatomical structures that simultaneously participate in nociception. The process that leads to pain begins with the stimulation of nociceptors. The reaction of finely myelinated Ad nociceptors occurs mainly to mechanical and thermal stimuli, while non-myelinated C-fiber nociceptors (polymodal) can also respond to chemical stimulation. Afferent impulses from nociceptors reach the neurons of the spinal horn and spinal cord. Roland's gelatinous (gelatinous) substance, also known as Plate II by B. Rexed, a highly specialized closed system that runs along the entire spinal cord behind the gray matter of the posterior horns, plays a significant role in modulating spinal cord pain. Roland's substance contains a large number of Hirke-Virchow cells, which contain neuroglia cells and neurons, which together with the neurons of the nucleus proprius form the first order neurons of the spinothalamic tract. Many μ and κ-opioid receptors, both presynaptic and postsynaptic, have been detected in these nerve cells. All of them are able to modulate pain of distal origin. For example, neuraxial administration of opioids leads to analgesia, primarily by acting in the dorsal horn of the spinal cord in a gelatinous substance, where they inhibit the release of excitatory neurotransmitters such as substance P and glutamate, and inhibit afferent neuronal transmission to the brain via hyperpores.

At the level of the gelatinous substance of the spinal cord, C fibers end. Thus, the cell bodies located here are part of the neural pathway, which relatively slowly transmits poorly localized pain. However, some fibers A, which quickly transmit information about localized pain) also end in a gelatinous substance, mainly through axons passing through this area to the nucleus proprius. Thus, there is a transverse interaction between the two pain pathways [3, 11].

Both described phylogenetically distinct systems of the spinothalamic tract, medial and lateral, transmit pain to neurons of the brain of the higher center. The medial system mainly consists of paleospinothalamic, spinosomencephalic, spinoreticular, spinohypothalamic fibers of the spinothalamic tract. These fibers are directed rostrally to the higher centers and end in the parabrachial nucleus, in the locus cæruleus of the reticular formation, periaqueductal gray matter of the midbrain, intralaminar and medial thalamic nuclei, thalamic ventral small cell nucleus, islet cortex [11]

Secondary somatosensory cortex, tonsils and hippocampus [11]. The medial system is involved in the affective and cognitive measurement of pain perception, is responsible for so-called pain memory and autonomic responses. In turn, the lateral system is formed by neospinothalamic, neotrigeminothalamic and cervical bundles and the bundle of the spinal

horn. In the higher centers, these fibers end in the lateral thalamus, its primary and secondary somatosensory area, parietal cover and islets (Fig. 1).
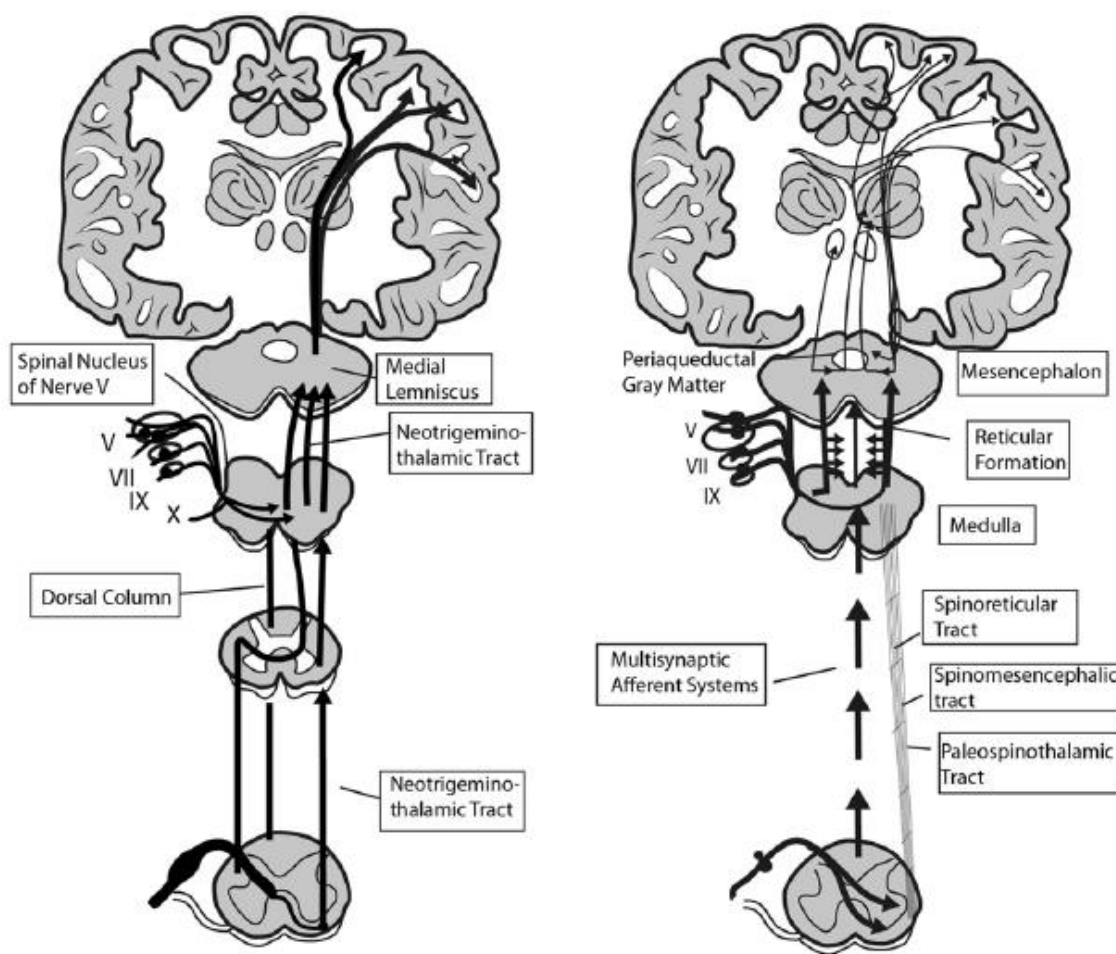


Fig. 1 Afferent nociceptive pathways (by Fil A. et al., 2013) [11]

The lateral system is important for the sensory-discriminant component of pain, because it provides information about the location and duration of pain [11, 12].

Descending pathways that begin in the brainstem and cerebral structures also play an important role in the integration and modulation of nociceptive information. They include serotonergic, noradrenergic and dopaminergic neurons capable of modulating the sensitivity of the neurons of the posterior horn of the spinal cord [11].

Levin O. and Makhnev S. identified four main types of chronic pain syndrome in PD [12]:

1. Nociceptive pain (musculoskeletal pain associated with rigidity, cramps and dyskinesis). This pain syndrome can be caused by the main symptoms of parkinsonism, such as muscle rigidity, dystonia, dyskinesia and cramps [12]. Muscle rigidity, depriving the muscle of physiological relaxation, leads to morphological changes in myofibrils, disruption

of ion exchange in the cell and, as a result, to the phenomena of aseptic inflammation and edema, causing microtraumatization of muscles, ligamentous apparatus and joint capsules. As a result, the habitual biomechanics of movement changes, the relationship between the state of muscle agonists and antagonists changes, which, in turn, can cause muscle pain associated with tonic disorders in the muscle [11, 12]. An important role in the formation of pain syndrome in Parkinson's disease is played by peripheral deafferentation, which is involved in the pathogenesis of sensitive (sensory) dysfunction [12].

2. Neuropathic (radicular (pseudo-radicular) pain, aka primary or central pain, pain associated with akathisia). Reflects dysfunction of the basal ganglia, which, through connections with cortical and stem structures, participate in the modulation of sensory, including nociceptive, afferentation [11]. As a result of the imbalance between the nociceptive and antinociceptive systems against the background of neurotransmitter disorders, the activity of the latter decreases with the preserved ascending nociceptive flow, as a result of which the pain threshold decreases [15].

3. Psychogenic pain (associated with affective disorders).

4. Combined pain.

In addition, these authors identified three groups of pain syndromes depending on dopaminergic stimulation. In the formation of this type of pain in Parkinson's disease, a certain role belongs to changes in the central dopaminergic mechanisms that are involved in the processing of pain information. Pain in patients with Parkinson's disease can occur against the background of both hypodopaminergic and hyperdopaminergic states [12]. Thus, the decrease in the intensity of the pain syndrome with the use of drugs with dopaminergic activity is a reflection of significant changes in the afferentation of pain impulses and their perception in the structures of the CNS in PD.

Conclusions:

1.      The pathogenesis of chronic pain in Parkinson disease is multimodal

2.      The approaches to pain management in PD patients primarily depend on the underlying cause

3.      The presence of chronic pain syndrome should always be considered as a reason for assessing the adequacy of antiparkinsonian therapy

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