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THE PATHOBIOLOGY OF CHRONIC PAIN. A POINT OF NEUROLOGIST'S VIEW

Abstract. *The current study has been performed in the specialized neurologic medical center. Analysis of main trends of chronic pain syndrome originating and development has been done, considering involving parts of both peripheral and central nervous systems. The incidence rate of chronic pain syndrome during certain period of time, its variants and intensity have been analyzed in patients with different neurological conditions and some comorbid diseases.*
Keywords. *chronic pain, pathobiology, physiology, nervous system.*

Introduction. Chronic pain occurs in 20-30% of the adult population [1, 2]. The Global Burden of Disease Study 2019 confirmed that the high prevalence of pain and associated diseases is the leading cause of disability and disease burden worldwide [1].

According to the International Association for the Study of Pain [3], chronic pain is pain that lasts longer than the normal tissue healing time, which, in the absence of other factors, is usually 3 months. There are many risk factors for chronic pain, including socio-demographic, psychological, clinical and biological [4, 5]. At the same time, the pathobiology of chronic pain remains a subject of scientific discussion.

Purpose of the study. The main goal of the current review is the analysis of main trends of chronic pain syndrome originating and development, considering involving parts of both peripheral and central nervous systems.

Materials and methods. The present research has been done in clinical units of Medical Center "Expert Health" (Odessa). The pain syndrome incidence rate has been detected in the Medical Center over the period of 2020 – 2021 (based on the exam of 446 patients). Chronic pain characteristics and its intensity have been assessed by Visual Analogue Scale, VAS (Likert scale). The literature search has been performed using PubMed, Embase, OVID, CYNAHL data bases by key words: chronic pain, pathobiology, nervous system. Statistical data processing has been done with MS Excel (Microsoft Inc., USA).

Results of study. On the time the initial visit chronic pain of different localization has been found in 159 patients (35.6%). Moderate intensity pain cases prevailed with the following result of 6.1± 0.3 according to VAS. In some cased the intensity of pain syndrome has been graded up to 8-9 points.

As the result of chronic pain study, all cased have been split into four main types: nociceptive, inflammatory, neuropathic and mixed (Fig. 1)

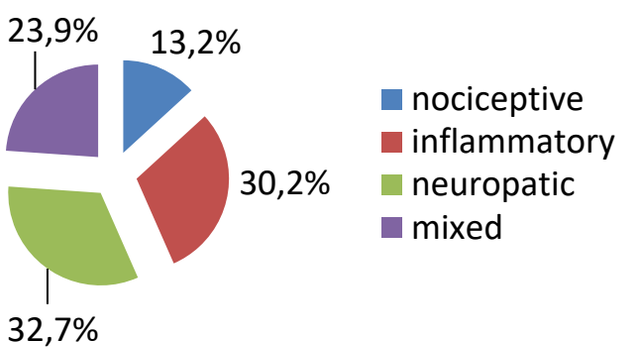

Figure 1. Chronic pain types in patients of Medical Center "Expert Health"

The most common cases of pain syndrome were inflammatory (30.2%) and neuropathic (32.7%). The rarest variant was true nociceptive pain - 21 cases or 13.2%.

The mentioned above chronical pain cases have been split into the following groups based on organ system:

musculoskeletal system diseases in 67 patients (42.1%);

chronical urinogenital pathology in 19 patients

Table

Main causes of the chronic pain syndrome [6]

Group of disorders	Diseases/Conditions
Musculoskeletal disorders	Osteoarthritis, Spondylosis, Rheumatoid arthritis, Lyme disease, Reiter syndrome, Disk herniation/facet osteoarthropathy, Fractures/compression fracture of lumbar vertebrae, Faulty or poor posture, Fibromyalgia, Polymyalgia rheumatica, Mechanical low back pain, Chronic coccygeal pain, Muscular strains and sprains, Pelvic floor myalgia (levator ani spasm), Piriformis syndrome, Rectus tendon strain, Hernias (e.g., obturator, sciatic, inguinal, femoral, spigelian, perineal, umbilical), Abdominal wall myofascial pain (trigger points), Chronic overuse syndromes (e.g., tendonitis, bursitis)
Neurologic disorders	Brachial plexus traction injury, Cervical radiculopathy, Thoracic outlet syndrome, Spinal stenosis, Arachnoiditis, Metabolic deficiency myalgias, Polymyositis, Neoplasia of spinal cord or sacral nerve, Cutaneous nerve entrapment in surgical scar, Postherpetic neuralgia (shingles), Neuralgia (e.g., iliohypogastric, ilioinguinal, or genitofemoral nerves), Polyneuropathies, Polyradiculoneuropathies, Mononeuritis multiplex, Chronic daily headaches, Muscle tension headaches, Chronic migraine, Temporomandibular joint dysfunction, Temporalis tendonitis, Atypical facial pain, Trigeminal neuralgia, Glossopharyngeal neuralgia, Nervus intermedius neuralgia, Sphenopalatine neuralgia, Referred dental or temporomandibular joint pain, Abdominal epilepsy, Abdominal migraine, Stroke (central poststroke pain)
Urologic disorders	Bladder neoplasm, Chronic urinary tract infection, Interstitial cystitis, Radiation cystitis, Recurrent cystitis, Recurrent urethritis, Urolithiasis, Uninhibited bladder contractions (detrusor-sphincter dyssynergia), Urethral diverticulum, Chronic urethral syndrome, Urethral carbuncle, Prostatitis, Urethral stricture, Testicular torsion, Peyronie disease
Gastrointestinal disorders	Chronic visceral pain syndrome, Gastroesophageal reflux, Peptic ulcer disease, Pancreatitis, Chronic intermittent bowel obstruction, Colitis, Chronic constipation, Diverticular disease, Inflammatory bowel disease, Irritable bowel syndrome
Reproductive disorders (extrauterine)	Endometriosis, Pelvic adhesions, Adnexal cysts, Chronic ectopic pregnancy, Chlamydial endometritis or salpingitis Endosalpingiosis, Ovarian retention syndrome (residual ovary syndrome), Ovarian remnant syndrome, Ovarian dystrophy or ovulatory pain, Pelvic congestion syndrome, Postoperative peritoneal cysts, Residual accessory ovary, Subacute salpingo-ophoritis, Tuberculous salpingitis
Reproductive disorders (uterine)	Adenomyosis, Chronic endometritis, Atypical dysmenorrhea or ovulatory pain, Cervical stenosis, Endometrial or cervical polyps, Leiomyomata, Symptomatic genital prolapse
Psychological disorders	Bipolar personality disorders, Depression, Porphyria, Sleep disturbances
Others	Cardiovascular disease (e.g., angina), Peripheral vascular disease, Chemotherapeutic, radiation, or surgical complications

(11.9%);

digestive system pathology in 13 patients (8.2%);

cardiovascular system diseases in 33 (20.8%);

At the same time, nervous system pathology has been diagnosed in 94 patients (59.1%). So, in the most cases several comorbid diseased have been detected.

Chronic pain syndrome has been found in 21 patients (13.2%) with Parkinson disease. Post-stroke chronical pain of central origin has been diagnosed in 8 patients (5.0%) and spasticity

related - in 16 patients (10%), complex regional pain syndrome - in 12 (7.5%). These observations correlate with data obtained earlier [19].

Chronic pain can accompany a big number of diseases of the musculoskeletal, digestive, urinary, reproductive and nervous systems [6-8]. The pathophysiology of chronic pain syndrome is multifactorial, complex and still understudied [9-12]. Some authors have suggested that chronic pain is based on a behavioral pattern in which the patient receives external or internal reinforcement. Indeed, patients with major depressive episodes, psychosomatic and conversion disorders tend to develop chronic pain syndrome [6, 10, 11]. However, this approach does not take into an account many other pathogenetic variants of pain syndrome.

The frequency of the above conditions in the population varies depending on risk factors, ethnics, age, level of medical care system development, treatment and preventive programs [1, 3, 6].

Discussion. Nociceptive pain is the response of sensory systems to actual or potentially harmful stimuli detected by nociceptors throughout the body. Inflammatory pain is associated with tissue damage and, as the result, inflammatory process, which can lead to reactions such as hyperalgesia, allodynia, and hyperpathy [9]. Neuropathic pain is a localized sensation of unpleasant discomfort caused by damage or disease of either the peripheral or central nervous system or both that persists after an initial injury or dysfunction. Neuropathic pain may be associated with allodynia, which refers to the sensitization of pain to stimuli that usually do not cause pain [6, 9, 10]. Hyperalgesia is related to an abnormally increased sensitivity to pain that is associated with hypersensitivity to stimuli. Primary hyperalgesia occurs directly in damaged tissues, while secondary hyperalgesia occurs in areas surrounding damaged tissues due to the binding of pain-related mediators to receptors around the injury site, causing sensitization of adjacent intact tissues to mechanical stimuli [9-11].

Afferent pathways of pain sensitivity are a complex sensory system that is activated to provide protective responses to harmful stimuli. Information about noxious stimuli is transmitted from nociceptors through the primary afferent fibers Aδ and C. These fibers have cell bodies located in the dorsal root ganglion and synapses with neurons of the spinal dorsal horn. Various neurotransmitters such as glutamate, calcitonin gene linked peptide (CGRP), and substance P are released as part of signaling [10]. Primary nociceptive afferents are transmitted through synapses to neurons in Rexed I and II plates and establish connections with neurons located deeper in the horn of the spinal cord, which play a role in signaling the presence, location and intensity of pain [9, 10]. Projection neurons from the dorsal horn intersect in the ventral commissure and ascend in the lateral spinothalamic tract to the thalamic ventral posterolateral nuclei. Finally, information is transmitted to the somatosensory cortex and periaqueductal gray matter (PAG) [10]. Nociceptive information is transmitted to areas of the brain, associated with memory and affective aspects of pain, such as the amygdala, hypothalamus, PAG, and nucleus accumbens (NAc), via the spino-reticular and spino-mesencephalic tracts [10]. These brain regions, including the somatosensory cortex, PAG, amygdala, hypothalamus, and NAc, are associated with supraspinal pain pathway responses [10]. Descending pain modulation systems include PAG and the rostral ventral brain (RVM). RVM is the main exit node in the downstream modulation of nociception. It receives input from the PAG and sends diffuse bilateral projections to the dorsal horn, terminating at multiple levels [10]. The ascending and descending pain pathways are shown in Figure 2.

In a study by Alonso-Blanco C. et al. in women, an association was found between the number of active myofascial trigger points (MTrP) and the intensity of spontaneous pain, as well as widespread mechanical hypersensitivity. Nociceptive inputs from these MTrPs may be associated with central sensitization [8]

A literature review conducted by Gupta A. et al. showed that among patients with chronic pain, primary sensorimotor structural and functional changes are more pronounced in women [13]. Men and women differed in the degree of changes in the insula and anterior cingulate gyrus, which manifested itself in different reactivity to emotional stimuli.

The development of pain is influenced by glial cells, which secrete neurotransmitters and molecules involved in pain pathways [9-11]. Glial cells initiate a series of signaling cascades that regulate pain processing at the spinal and supraspinal levels. Glial cells also release inflammatory cytokines and chemokines that can facilitate pain transmission through binding to neuronal glutamate receptors. Bidirectional interactions between neurons and glia affect the processing, expression and transmission of pain and play a crucial role in the development and maintenance of pain [10].

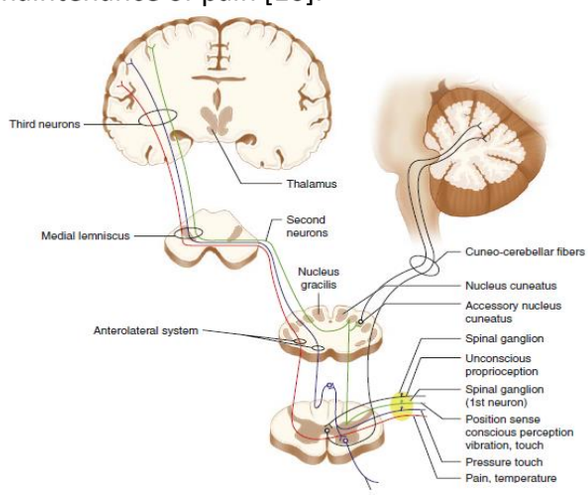

Figure 2. Pain pathways

Central sensitization is triggered by increased nociceptive effects caused by either trauma or inflammation and is the result of physiological plasticity and long-term changes in the CNS [10]. An increase in the responses of primary afferent fibers, as well as increased spontaneous activity and excitability of neurons in the dorsal horn and areas of the receptive field, are associated with central sensitization [10]. The central sensitization mechanism involves glutamate signaling via postsynaptic N-methyl-D-aspartate (NMDA) receptors. Activation of NMDA receptors leads to the opening of ion channels and calcium influx. This calcium flow plays a critical role in the synaptic plasticity of both excitatory and inhibitory synapses. Synaptic plasticity can increase the sensitivity of the central nociceptive system, resulting in increased sensitivity to pain and persistent pain [9-11].

The thalamus is commonly considered as a sensory relay center, but there is strong evidence that it plays an important role in higher cognitive functions [10]. There is a continuous complex afferent-efferent interaction between the nuclei of the thalamus and the cerebral cortex. Correct input from thalamic nuclei receives positive feedback from the higher cortical regions, while unnecessary input is suppressed [10].

There are 50-60 known nuclei of the thalamus. The ventral-posterior group of nuclei is the main somatosensory relay structure. It receives afferent information from the spino-thalamic tract, medial loop and trigemino-thalamic tract, and projects it onto the somatosensory cortex and reticular formation [10].

There is an evidence that neurons in the ventral-posterior thalamus respond to tissue-damaging stimuli and have characteristics similar to those of nociceptive-specific neurons in the dorsal horn of the spinal cord. The medial thalamus also receives impulses from the spinothalamic tracts. The more the medial nuclei are projected onto wide areas of the cerebral cortex, the more they are involved in the structures of the limbic system that control motivation and emotions; therefore, they probably play a role in the motivational-affective aspects of chronic pain, but not in its sensory-discriminatory aspects. However, nociceptive neurons of the ventral-posterior group of thalamic nuclei are projected onto the primary somatosensory cortex, which suggests their participation in the processing of sensory signals.

The symptom complex of thalamic pain stands apart in chronic pain syndrome. Any damage to the thalamus affects the contralateral part of the body. Initially, lesions of the thalamus result in hemianesthesia. Subsequently, patients describe the pain as a burning sensation that is exacerbated by emotional stress and minimal sensory stimulation of the skin and mucous membranes. In some cases, in particular in acute cerebrovascular event in the thalamus, caused by thrombosis of the thalamo-geniculate artery with ischemic damage to the ventral posterolateral nucleus of the thalamus, Dejerine-Russi syndrome occurs, while chronic pain is emotionally colored. Short-term hemiplegia or hemiparesis, sometimes with subsequent impaired coordination of movements on this side after the disappearance of paresis, is accompanied by a pronounced impair of cutaneous and deep sensitivity ipsilaterally, at the same time there are

unbearable, burning, diffuse, extremely intense pain in this half of the body, unilateral hyperpathy (perception of any touch and others usually painless tactile sensations as extremely painful), as well as pronounced mood swings or depression, up to suicidal thoughts or attempts. Dejerine-Russi syndrome is also possible with either metastatic or primary tumor lesions of the thalamus [10].

In some cases, the phenomenon of the "thalamic hand" of Foix-Hilleman is observed, in which a stable pathological position of the fingers of the hand is formed in the way of "main d'accoucher" or " saucer-like hand". At the same time, the main phalanges are moderately bent, the middle and terminal ones are completely unbent. Choreoathetosic distal hyperkinesis is often observed.

Foix-Chiari-Niculescu syndrome, or the upper red nucleus syndrome, is also a case of interest. It manifests on one side with cerebellar disorders, choreoathetosis, sensory disorders, and sometimes "thalamic arm" and thalamic pain. These indicate focal lesions of the anterior part of the midbrain tectum with involvement the upper small-cell part of the red nucleus, spreading in the rostral direction to the thalamus and disrupting the connection of the red nucleus with other formations of the extrapyramidal system.

Nociceptive pain in Parkinson's disease (PD) is very common (40-90% of all cases of pain in this disorder) [10, 14]. Nociceptive pain associated with PD could be musculoskeletal and visceral pain. Musculoskeletal pain in patients with PD and other types of parkinsonism usually is an outcome of abnormal posture, rigidity and akinesia, resulting in dystonia and chronic pain. Deterioration of dystonia in the early morning is typical, when dopaminergic stimulation is low, and akinesia and rigidity are more pronounced. Dystonia often presents as focal dystonia with plantar flexion and inversion of the foot. Another common type of nociceptive pain is visceral pain, which often accompanies constipation syndrome. Intestinal function in PD patients is influenced by several factors, including autonomic failure and the degree of intestinal plexus involvement. Dystonic contractions of the anal sphincter muscles can lead to parcopresis and tenesmus [14].

Neuropathic pain associated with PD is represented by radicular and central pain [10, 14]. Radicular pain has a significantly higher prevalence in PD patients than in the general population (14–35% versus 10%) [14]. This high frequency probably reflects damage to the lumbar disc structure due to festination, kyphosis, and dystonia. Central pain associated with PD is a relatively rare condition (4-10% of patients) [14]. Basically, this pain manifests ipsilaterally to the side of the body with predominant motor symptoms. Unlike "classic" central pain, in PD this pain is not associated with severe sensory deficits [10, 14]. Most researchers believe that the central type of pain in PD arises directly from dysfunction of the basal ganglia, which alters the sensory processing of nociceptive inputs [9-11].

Another group of effects is associated with inflammatory changes in tissues and organs. Inflammation itself causes pain, but the nerve damage resulting from mechanical or iatrogenic trauma, metabolic or autoimmune disorders, cancer, and chemotherapy can cause neuropathic pain [10, 12]. Excitation of primary neurons due to prolonged inflammation induces a pathological response that persists after a period of tissue repair, constantly stimulating nociceptive pathways and thus causing chronic pain with changes in ion channels, receptors and nerve synapses. The distribution of neurotransmitters and neuromediators allows peripheral and central neurons to reach the depolarization threshold earlier in order to cause an increase in ectopic discharges and activation of nearby cells with an increase in the intensity of chronic pain [10].

The pathophysiological mechanisms of neurons are integrated with the immunological response, thus neuropathic pain can be considered as a complex neuroimmune disorder [10, 11]. Patients with complex regional pain, peripheral neuropathy, and neuropathic pain associated with spinal cord injury syndrome have elevated serum levels of IL-4, IL-6, and TNF-α, as well as decreased levels of serum IL-10 [12]. Increased serum levels of IL-1β, IL-6, IL-2, TNF-α and IFN-γ enhance the intensity of chronic pain [10, 12]. Therefore, inflammatory and allogeneic processes are maintained by a complex balance between the cytokines produced by the cells (due to both pro-inflammatory and anti-inflammatory

molecules) and the structures of the nervous system.

In oncological diseases chronic pain syndrome has a multimodal character [12, 15]. Traditionally, the following main causes of pain syndromes in cancer patients are distinguished [15]:

- caused by the tumor itself (damage to bones, soft tissues, skin, internal organs, occlusion of blood vessels, digestive tract, etc.);
- due to complications of the tumor process (pathological fracture, necrosis, ulceration, inflammation, infection, thrombosis);
- due to paraneoplastic syndrome (arthro-, neuro- and myopathy);
- due to asthenization (bedsores, trophic ulcers, constipation);
- associated with cancer treatment;
- due to complications of surgical treatment (phantom pain, pain with adhesions, scars, anastomositis, edema),
- due to complications of chemotherapy (stomatitis, polyneuropathy, generalized myalgia, aseptic necrosis, arthralgia),
- due to complications of radiation therapy (damage to the skin, bones, fibrosis, plexitis, neuritis, myelopathy, etc.).

IL-6, TNF-α and IL1-β, produced by macrophages, are cytokines that increase chronic pain. According to some studies, increased TNF-α expression is associated with thermal hyperalgesia, mechanical allodynia and pain-related hypersensitivity. In cancer patients TNF-α can also increase the K + ion conductivity of the membrane regardless of voltage, which leads to general hyperexcitability of neurons and, consequently, neuropathic pain. TNF-α induces the release of glial mediators, which enhance endocytosis of the GABA receptors, followed by the decrease in the inhibitory modulation of the GABA-ergic system. In this case, long-term potentiation takes place, which is a physiological mechanism for strengthening the neural circuit, which is involved in many nerve functions [4, 9-11].

Thus, the involvement of the structures of the peripheral and central nervous system is crucial in the development of chronic pain syndrome, regardless of which pathological process is primary in each case. Underestimation of the role of the patient's psycho-emotional state and the severity of organic changes in the central nervous system leads to an aggravation of the pain syndrome severity, significantly worsens the quality of life and prognosis.

Conclusions.

1. In a specialized medical center the incidence rate of chronic pain syndrome is at least 35%

2. Among the cases of chronic pain syndrome the ones with moderate pain intensity prevail.

3. Diseases of the nervous system have been observed in 94 patients (59.1%). In all cases the presence of several comorbid diseases has been typical.

Prospects for further research. The prospects for further research are related to the study of the mechanisms of the chronic post-stroke pain onset in patients of different ages.

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