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ACUTE PAIN SYNDROMES IN INJURIES TO THE NERVES AND PLEXUSES OF THE LIMBS

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Injuries of peripheral nerves and plexuses cause serious disorders in the affected limbs. Unfortunately, the frequency of nerve injuries and limb plexuses is steadily increasing in our country, due to hostilities, which emphasizes the extreme relevance of this pathology.

The aim *of the review is to consider the current data on pathophysiological mechanisms, clinical manifestations, and treatment of acute pain syndromes in patients with injuries of peripheral nerves and limb plexuses.*

Materials and methods. *Scientific databases PubMed, Google Scholar, Scopus, Cochrane Library, as well as the materials of the International Association for the study of pain were used to search for sources of research information. The main studies were found in Pubmed, Google Scholar and materials of the International Association for the study of pain and made up 191 sources of information, 150 of which were excluded from the review due to insufficient data on pathophysiological mechanisms, clinical manifestations, and treatment of pain syndromes in patients with damage to the nerves and plexuses of the limbs, thus 41 sources of information formed the basis of the review.*

Results: *Brachial plexus and peripheral nerve injuries can be associated with any combination of nociceptive, neuropathic, phantom limb pain, and even complex regional pain syndromes. Acute neuropathic pain is an under-recognized condition, often difficult to treat and can progress to persistent pain and disability. Neuropathic pain develops because the main damage affects the somatosensory system. It is caused by peripheral nerve damage and associated changes in the central nervous system. The first line of pharmacological treatment for neuropathic pain according to current guidelines is anticonvulsant drugs that affect neuronal calcium channels, as well as tri- and tetracyclic antidepressants and selective serotonin/norepinephrine reuptake inhibitors.*

Conclusions: *At the current stage, progress has been made in understanding the mechanisms of development of the pathological condition and in the development of therapeutic approaches, however, the chronicity of pain syndrome in patients with damage to the nerves and plexuses of the limbs is still high, which requires further research to develop complex pathogenetic therapy and better understanding of the mechanisms pain in this category of patients*

Keywords: *pain, pain syndrome, neuropathic pain, nociceptive pain, injuries to nerves and plexuses of the limbs, neuropathies and plexopathies, treatment of neuropathic pain syndrome*

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1. Introduction

Injuries of peripheral nerves and plexuses cause serious disorders in the affected limbs. Unfortunately, the frequency of nerve injuries and limb plexuses is steadily increasing in our country, due to hostilities, which emphasizes the extreme relevance of this pathology. Diagnosis and treatment of pain in patients with peripheral nerve damage is a difficult task due to the peculiarities of pathogenesis and the variety of clinical manifestations. Acute pain is a new, recent pain inextricably linked to the damage that caused it, usually a symptom of a disease and an emergency. The percentage of patients experiencing neuropathic pain due to peripheral nerve and plexus injuries varies from 67 to 95 % depending on the study [1]. Numerous guidelines are available for neuropathic pain, but they are not always implemented in clinical practice [2–4].

Optimal treatment of neuropathic pain is a clinical necessity and goes far beyond simple "pain control" [5]. Since most patients with nerve and plexus injuries have acute neuropathic pain, we pay special attention to this type of pain.

The International Association for the Study of Pain (IASP) in its terminology section defines pain as an unpleasant sensory and emotional experience with actual or potential damage [6].

Willis et al. developed the theory of the specificity of the pain syndrome, which is based on the existence of

special pain receptors (nociceptors) that cause a direct sensation of pain in the corresponding parts of the body [7]. Currently, thanks to the work of various authors, an idea has been formed about the "antinociceptive system", which produces endogenous peptides that control pain sensitivity. Thus, modern ideas about pain are based on the assumption of the interaction of nociceptive and antinociceptive systems. In the brain, the structures of the antinonceceptive system are represented in various ways, which are included in various neurotransmitter mechanisms (norepinephrine, serotonin, opioids, dopamine), while working not in isolation, but interacting with each other and with other systems, they regulate not only pain sensitivity, but also autonomic, motor, neuroendocrine, emotional and behavioural manifestations of pain associated with pain [5, 7]. The study of the interaction of nociceptive and antinociceptive systems and the peculiarity of their functioning is an urgent task of modern neurology, therefore it requires further research in order to develop highly effective therapy to combat pain syndrome.

The aim of the review is to consider the current data on pathophysiological mechanisms, clinical manifestations, and treatment of acute pain syndromes in patients with injuries of peripheral nerves and limb plexuses.

2. Materials and methods

Scientific databases PubMed, Google Scholar, Scopus, Cochrane Library, as well as the materials of the International Association for the study of pain were used to search for sources of research information. The search queries included the following keywords: "pain syndromes in the case of damage to the nerves of the limbs", "neuropathic pain", "nociceptive pain", "pain in the case of nerve and plexus injuries". The main studies were found in Pubmed, Google Scholar and materials of the International Association for the study of pain and made up 191 sources of information, 150 of which were excluded from the review due to insufficient informativeness of data on pathophysiological mechanisms, clinical manifestations and treatment of pain syndromes in patients with nerve and plexus injuries, thus 41 sources of information formed the basis of the review.

3. Results

Damage to the brachial plexus and peripheral nerves can be associated with any combination of nociceptive, neuropathic, phantom limb pain syndromes, and even complex regional pain syndrome (CRPS) [1, 8].

Nociceptive pain is a protective physiological reaction of the nervous system, important for preserving the integrity of the body, detecting a threat and real tissue damage [9, 10]. Nociceptive pain is associated with direct damage to the musculoskeletal system and with muscle dysfunction secondary to myofascial syndromes characterized by painful spasms and muscle contractures [1, 8].

Neuropathic pain develops because the main damage affects the somatosensory system. It is caused by peripheral nerve damage and associated changes in the central nervous system. Neuropathic pain can appear immediately or several months after a traumatic injury, and its intensity usually increases over time due to mechanisms of plasticity of the sympathetic nervous system [11]. In addition, "nociceptive pain" is defined as the activation of nociceptors in the presence of threatened or actual damage to non-neural tissue, that is, a normally functioning somatosensory nervous system is preserved, in contrast to "neuropathic pain", which occurs as a lesion or disease of the somatosensory system. Clifford and Woolf emphasize the manifestation as "spontaneous pain independent of a stimulus" compared to "pain caused by a stimulus" [12]. This is an important distinction, as non-traumatic peripheral neuropathic pain can also arise from common diseases such as diabetic neuropathy, chemotherapy-induced polyneuropathy, and postherpetic neuralgia, which are important to differentiate in terms of treatment planning [13, 14].

Post-traumatic pain syndrome develops because of damage to peripheral nerves and is included in the structure of CRPS type II. Post-traumatic pain syndrome is defined as a complication of soft tissue injuries and limb bone fractures, in which persistent intense pain, vegetative, vascular, and trophic disorders, as well as osteoporosis occur as a result of neurodystrophic disorders [15]. The pathogenesis of post-traumatic pain syndrome consists of a change in the activity of the sympathetic nervous system, irritation of peripheral nociceptors, i.e. nociceptive component, and damage to nerve conductors, which leads to the emergence of a neuropathic component. Vegetative dysfunction is the cause of persistent disturbances of local blood circulation, which at the early stage of the disease are expressed in neurogenic vasoconstriction of blood vessels and dilatation of precapillary sphincters. At the next stage, characterized by functional exhaustion of the sympathetic nervous system, there is a neurogenic weakening of the tone of microvessels, especially venules. The developing vascular dystonia leads to a violation of the permeability of the capillary walls. Microcirculatory disorders, tissue hypoxia and acidosis develop in the affected segment.

It is also known that the nature of the previous injury does not determine the degree of development of post-traumatic pain syndrome [16]. Nociceptive pain is caused by the activation of nociceptors in response to injury, corresponds to the degree of tissue destruction and the duration of healing.

Neuropathic pain was first defined by the International Association for the Study of Pain (IASP) as pain initiated or caused by a primary lesion or dysfunction of the nervous system [17]. This definition was revised in 2008 by the IASP Special Interest Group on Neuropathic Pain and adopted in 2011 as “pain caused by a lesion or disease of the somatosensory nervous system” [18]. However, the optimal definition of neuropathic pain remains elusive because peripheral or central nervous system lesions can occur in patients with concomitant neurologic dysfunction, and pain occurs only in a subset of these patients. In other words, nerve damage does not mean that the patient has neuropathic pain [19]. Thus, the presence of a neurological lesion or neurological disease does not guarantee the presence of neuropathic pain, which seems to be more related to induced changes in the peripheral and central nervous systems, such as changes in pain modulation systems, central sensitization, and others. The lack of clear definitions hinders progress in the classification and evaluation of neuropathic pain [20].

Acute neuropathic pain (ANP) is an under-recognized condition, often difficult to treat and can progress to persistent pain and disability [21]. According to Colloca et al. neuropathic pain is caused by damage or disease of the somatosensory system, including peripheral fibers (Aβ, Aδ and C fibers) and central neurons affects as many as 7–10 % of the population [22].

Neuropathic pain symptoms can be "negative", namely hypoesthesia, thermal or mechanical anesthesia, hypalgesia, and loss of vibration sensation. Also, symptoms can be "positive", including paresthesia, dysesthesia, hyperesthesia, allodynia [1, 9]. Neuropathic pain arising from damage to structures of the peripheral nervous system is characterized by a number of features: the pain is intense, spontaneous or constant; elimination of the pathogenic factor, as a rule, does not ensure complete cessation or reduction of pain intensity; pain sensations can increase under the influence of various factors - motor activity, strong emotional reactions, change in weather conditions; in most patients with neuropathic pain syndrome, psychoemotional personality changes are noted.

According to the pathogenesis, Wallerian degeneration occurs after damage to the axon in the distal part of the nerve. In a study by Quintao et al. it was established that the axon and its myelin sheath undergo degradation, after which the tissue is infiltrated by inflammatory cells that release pro-inflammatory and nerve growth factors that enhance the perception of pain stimuli and lower the pain threshold [10]. Damaged axons and cell bodies in the dorsal root ganglia undergo an intrinsic increase in electrical excitability, thus spontaneously transmitting impulses to the CNS (primary neuropathic pain signal) and maintaining central sensitization. Central sensitization is a mechanism of pain intensification and chronicity, which increases the degree of damage to the somatosensory system. It involves glutamate sensitization of N-methyl-D-aspartate (NMDA) receptors in the spinal cord and with long-term changes [9, 23]. It is believed to increase sensory endings in the skin and deep tissues, causing tactile allodynia, and increasing spontaneous dysesthesia and pain. It is this phenomenon, along with deafferentation, that distinguishes peripheral neuropathic pain from other types of pain [24].

In their work, Devor and Wall presented observations of peripheral nerve damage that leads to plasticity and reorganization of cells in the posterior horn. An important aspect is the depolarization of voltage-gated sodium channels, which leads to the spontaneous activity of the action potential with an inappropriately high frequency, which contributes to the inflammatory process and peripheral sensitization, contributing to the positive sensory phenomenon of spontaneous pain, allodynia, and hyperalgesia [25].

According to Samii M et al., Zheng Z et al., Chivukula S et al. the hyperactive state of spinal cord neurons due to the lack of inhibition caused by structural changes in the spinal cord may explain persistent pain, regardless of the initial peripheral mechanisms responsible for it [26–28]. Bertelli J et al. claim that the development of pain is mediated by non-avulsive roots, which may explain the reduction in pain observed after primary, early repair of brachial plexus injuries [29].

Recent functional imaging work supports cortical and subcortical neuroplasticity after peripheral nervous system injuries, and the resulting neuropathic pain is thought to be deafferented and age-related [30]. In models, these include adaptation of cerebral plasticity, reduced intracortical inhibition, and later axon misrouting with disruption of cortical maps after nerve regeneration, when cortical areas adjacent to damaged cortical representation areas expand and occupy the previously damaged site [31, 32].

Diagnosis of acute pain syndromes in the case of peripheral nerve damage consists of an anamnestic component, clinical and neurological examination data using rating scales and questionnaires to determine the intensity and type of pain, for example, visual analogue scale (VAS), McGill test, DN4, PainDetect. In addition, electroneuromyography techniques for assessing nerve conduction and verifying peripheral nerve damage are included in the diagnostic algorithm as an instrumental examination method.

The main methods used in the treatment of acute pain syndromes due to damage to peripheral nerves and plexuses of the extremities are [33, 34]:

Neurosurgical:

– neurolysis;

– nerve suture;

– neuroticism;

– medical blockades, etc.

Medication (depending on the type of pain):

– analgesics;

– nonsteroidal anti-inflammatory drugs (NSAIDs);

– anticonvulsant drugs;

– tricyclic antidepressants;

– selective serotonin and norepinephrine uptake inhibitors, etc.

Physiotherapy:

– magnetic therapy;

– antipain electrostimulation;

– low-intensity laser therapy, etc.

Data from scientific publications indicate the ineffectiveness of generally accepted neurosurgical treatment methods in 15–20 % of patients. Surgical intervention is accompanied by technical difficulties, frequent complications, and, in addition, nerve recovery may be incomplete. Intracanal blockades do not always lead to the expected result, in addition, a few complications may occur, so the best methods of treatment of post-traumatic neuropathies and associated pain syndrome, especially in the early stages, remain conservative [34]. Nonsteroidal anti-inflammatory drugs are an invariable component of drug treatment of nociceptive pain caused by peripheral nerve injury due to their ability to influence pain impulses at all levels of afferent transmission – from peripheral nociceptors to sensitive brain centers. The mechanism of action of NSAIDs consists in inhibiting the synthesis of prostaglandins due to the inhibition of the key enzyme – cyclooxygenase (COX), which leads to a slowdown in the production of prostaglandin E2, thromboxane A2, as well as a decrease in the level of leukotrienes, kinins, histamine, serotonin and other inflammatory mediators [35].

Pharmacological treatment of neuropathic pain is aimed at the use of drugs acting on the central nervous system. Tricyclic antidepressants (amitriptyline, nortriptyline), calcium channel ligands (pregabalin, gabapentin), other anticonvulsant drugs (carbamazepine, clonazepam) and neuroleptic drugs have a strong analgesic effect on neuropathic pain [36]. Based on the pharmacological principle of potentiation of synergism, it is recommended to combine two or more drugs. A combination of a tricyclic antidepressant and pregabalin or gabapentin is considered first-line pharmaceutical treatment, while some opioids, other antidepressants, and other anticonvulsants are prescribed as second-line therapy [37, 38]. Treatment usually starts with gabapentin or pregabalin, alone or with a tricyclic antidepressant.

In 2019, the German Neurological Society published a guideline for the diagnosis and treatment of neuropathic pain, in which it is recommended that the diagnosis of neuropathic pain be based on typical symptoms and signs of neuropathic pain, namely positive sensory symptoms (hyperalgesia, allodynia, hyperesthesia) and negative sensory symptoms (hypesthesia, hypalgesia). It is also stated that damage to the somatosensory system must be demonstrated by neurological examination and confirmed by instrumental examination, as a screening tool or to assess the severity of neuropathic pain, questionnaires and scales can be used. Anticonvulsants that affect neuronal calcium channels (gabapentin, pregabalin), as well as tri- and tetracyclic antidepressants and a selective serotonin/norepinephrine reuptake inhibitor are recommended as the first choice for pharmacological treatment in the guideline [39].

Despite ongoing treatment, the chronicity of neuropathic pain syndrome remains high. If there is no improvement after 6–8 weeks, other drugs should be prescribed, including other anticonvulsants such as carbamazepine and lamotrigine, second-line antidepressants such as venlafaxine and duloxetine, and ultimately an opioid analgesic [37, 40].

Study limitations. In the study, careful attention is paid to neuropathic pain, to a lesser extent to nociceptive pain, as well as the peculiarities of treatment tactics in patients with persistent severe pain syndromes due to damage to nerves and plexuses of the extremities, which is a limitation of this study.

Prospects for further research. We plan to conduct an extended study taking into account the main features of early diagnosis and the need for comprehensive correction of pain syndromes in patients with nerve and plexus injuries.

5. Conclusions

Thus, the treatment of pain syndromes associated with damage to the nerves and plexuses of the extremities remains an urgent and difficult clinical task, at the current stage, progress has been made in understanding the mechanisms of the development of the pathological condition and in the development of therapeutic approaches, however, the chronicity of pain syndrome in patients with damage to the nerves and plexuses extremities is still high, which calls for further research aimed at developing complex pathogenetic therapy and a better understanding of pain mechanisms in this category of patients.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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The manuscript has no associated data.

Use of artificial intelligence technologies

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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