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Peripheral nerve traction injury. Literature review

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Traction injury of the peripheral nerve (TIPN) is an injury that occurs as a result of stretching the nerve beyond its normal elastic properties. An analysis of the available literature has revealed the following. TIPN is the most common type of severe nerve injury in the setting of road traffic accidents, catatrauma, gunshot wounds, birth injuries, etc. The dynamics of TIPN during fast and slow stretching is the same and includes three phases: elastic, inelastic and tearing. The limits of elastic stretching of the nerve are determined by the degree of tortuosity of myelinated fibers and the elasticity of the connective tissue framework of the nerve. Stretching of the nerve beyond its elastic limits is characterized by rupture of axons and endoneurial sheaths, including at a considerable distance from the epicenter of pathomorphological changes, which determines the severity of the injury and the impossibility of effective nerve autoregeneration. The force of stretching and the direction of its application to the nerve trunk determine the severity of TIPN. The degree of nerve stretching varies along its length and reaches a maximum in the periarticular areas. A fairly moderate stretching of the nerve can lead to a noticeable change in the conductivity of electrical impulses. Unlike other localized types of nerve injury, the pattern of pathomorphological changes in TIPN includes various forms of damage to structural elements. Understanding the pathophysiology of TIPN is a prerequisite for the development of optimal treatment of this type of injury.

Keywords: *peripheral nerve injury; traction mechanism of injury; pathogenesis; biomechanics of injury; classification of injury degrees*

Introduction

Peripheral nerve injuries (PNIs) result in a variety of symptoms depending on the degree of severity and the site of application of the traumatic factor. Despite significant progress in understanding the mechanisms of nerve injury and regeneration, effective treatment methods are insufficient to fully restore functions. Symptoms of mechanical nerve injury are impaired sensation, motor or autonomic function disorders, pain. Sustained disability of patients who have suffered moderate to severe injuries prevents return to daily life in 28–70% of cases [1,2]. It is not uncommon for PNI patients to be very limited in motor activity and performance of activities of daily living such as cleaning, food consumption, and personal hygiene. In addition, most patients after PNI have pain syndrome, which can be very intense and prolonged [3]. This leads to impaired quality of life and a feeling of social isolation. Treatment of pain syndromes is a definitely unsolved problem, despite advances in modern pharmacology, thorough knowledge of the physiology and anatomy of pain [4]. In addition to treatment and physical rehabilitation, attention should be paid to the psychological state of patients with PNI and their social adaptation. Sometimes a combination of techniques is required to restore sensory and motor function. It is important to diagnose PNI as soon as

possible, because it improves the treatment outcomes and reduces the risk of complications.

In the United States of America, about 18,000 cases of PNI are reported annually representing 1.5–6.0% of the total number of injuries [5,6]. These are peacetime statistical data, but in wartime, the injury rate increases, which makes the problem of PNI relevant for military and medical workers. In the post-traumatic period, the quality of life of patients depends primarily on the severity of the injury, timeliness and quality of medical care.

The most common mechanism of severe nerve injury in clinical practice is traction injury of the peripheral nerve (TIPN) [7] arising from road traffic accidents, catatraumas, gunshot wounds, as well as birth trauma [8]. According to research data, the prevalence of brachial plexus injury during labor is 0.4–3.8 cases per 1000 deliveries [9]. Several factors lead to brachial plexus injury during delivery: large fetal size, length of labor, use of forceps or vacuum extractor, breech presentation of the fetus, maternal health status, particularly the presence of gestational diabetes mellitus or obesity, which increases the risk of large fetal size, abnormalities development of the uterus and birth canal, birth trauma during previous births [10–12].



Proximal C5-C6 paralysis (Erb-Duchenne palsy) is the most common type of paralysis, accounting for 50-60% of the total number of cases. In about 30% of cases, the lesion extends to the C7 root. Total paralysis of C5-D1 roots, which is an extremely severe condition, occurs in 15-20% of cases [13]. Distal C8-T1 root palsy (Dejerine-Klumpke palsy) occurs in less than 2% of cases. This type of paralysis can occur during delivery in case of breech presentation [14]. It is important to remember that most cases of brachial plexus injury during delivery can be avoided with proper obstetric care and appropriate interventions when necessary.

Although peripheral nerves have good regenerative capacity, regeneration may be inadequate due to the severity of the injury and its biomechanical features, which may result in limited or failed regeneration. During histological studies of specimens of injured nerves, intraneural fibrous scar is often found to impair the regeneration process. Therefore, understanding the pathogenesis and morphofunctional features of the nerve after traction injury is important for improving its treatment.

The structure of the peripheral nerve

The peripheral nerve (PN) is formed from axons that provide motor, sensory and autonomic functions. Each axon is covered with Schwann cells (SCs), which are divided into myelinating and non-myelinating cells [15]. Non-myelinating SCs simultaneously cover several axons with a single layer of neurolemma, such axons are called unmyelinated. Transmission of the electrical impulse in these fibers is slow, from 0.1 to 2.0 m/s. In myelinated fibers, each SC spins around the axon, forming a "duplicate" of the neurolemma - the mesaxon. The multi-layered winding of the mesaxon around the axon entails the formation of a myelin sheath. The myelin sheath has areas of axon exposure called "nodes of Ranvier". Many sodium channels are located in the node of Ranvier, where action potentials can be generated and renewed. When the axon membrane is excited, the generated electrical impulse cannot pass through the highly resistant myelin sheath, so the impulse goes to the surface of the myelinated fiber in the node of Ranvier. This depolarizes the axonal membrane of the next node, and thus the depolarization spreads rapidly along the myelinated fiber, jumping from node to node (saltatory). The length of the internodal sections is proportional to the diameter of the fiber. The larger the diameter and the longer the intervals, the higher the velocity of excitation conduction. In myelinated fibers, the conduction velocity of an electrical impulse usually ranges from 3 to 120 m/s [16,17].

Two types of transport are contained within the axon: anterograde (from the neuron to the target organ) and retrograde (from the periphery to the neuron body). There are two types of anterograde transport - fast and slow. Fast transport of vesicles, organelles, membrane proteins, secretory polypeptides, neurotransmitters and endoplasmic reticulum components is carried out by the kinesin protein at a rate of 100 to 400 mm/day. Microtubules, neurofibrils, cytoskeletal proteins and other proteins are moved by slow anterograde transport, which has two components (*a* (0.2-2.5 mm/day) and *b* (5.0-6.0 mm/day)). Endosomes, growth factors, trophic factors, damaged organelles, viruses, and some toxins are transported by retrograde

transport. These components are transported with the help of the dynein protein at a rate of 200 to 270 mm/day [18,19].

Externally, myelinated and unmyelinated axons are covered with endoneurium, a protective sheath that surrounds individual nerve fibers and contains fluid (endoneurial fluid). The latter has a low protein content and is similar to the cerebrospinal fluid of the central nervous system. If a peripheral nerve is damaged, the endoneurial fluid may leak into the surrounding tissues. This process can be detected by magnetic resonance neurography, which helps to determine the location of peripheral nerve injuries [20]. The endoneurium is formed from endoneurial cells. The endoneurial canal with closed nerve fibers is united in groups called "nerve bundles" [21]. The layer covering the nerve bundles is called "perineurium". The perineurium contains connective tissue with a distinct lamellar structure consisting of one or more concentric layers. The perineurium is composed of perineurial cells, which are a type of epithelioid myofibroblasts. Externally, the PN is enveloped by the epineurium - a protective layer of dense connective tissue that maintains the structure and protects the PN from external influences [22, 23]. The epineurium contains blood vessels that supply the nerve [24], as well as lymphocytes and fibroblasts that promote the synthesis of collagen fibers. In addition to providing structural support, lymphocytes and fibroblasts play a vital role in the maintenance and repair of surrounding tissues [25]. Due to the dense structure of the epineurium, the nerve is easily separated from the surrounding tissues. Inside the nerve, axon bundles can be arranged in different ways, their topography can be monofascicular or oligofascicular. The structure of the nerve varies along its entire length, as axon bundles repeatedly branch and unite [26]. In the areas of the joints, the nerve is rich in connective tissue, and a larger number of vessels are located around it [27]. The elasticity of the epineurium and the wave-like direction of axon bundles within it allow the nerve to stretch during physiological joint movements without losing the function of the PN [28].

The classification of PN injury depends on the integrity of the structures forming the PN trunk.

Classification of nerve injuries

The classification according to Sunderland and Seddon [29] is the most widely used when describing the degree of PN injury. Seddon classified traumatic nerve injury into three classes:

- I. Neurapraxia is a temporary physiological block of conduction in a nerve fiber due to its integrity.
- II. Axonotmesis - violation of axon integrity with preservation of the surrounding sheaths.
- III. Neurotmesis is a complete rupture of a peripheral nerve.

In 1951, S. Sunderland expanded the Seddon classification to five degrees: Neurapraxia corresponds to class I according to Seddon, the second grade is class II according to Seddon, the third grade characterizes a violation of axon integrity and endoneurium, with the fourth grade, the perineurium is interrupted together with the endoneurium and axon, fifth grade - complete nerve transection. Full restoration of the function of the PN is possible with injuries of the I and II grades, with injuries of the III grade, partial restoration is possible,

but surgery may be required. Grade IV and V injuries require surgical intervention [30].

Peripheral nerve response to injury

When a nerve is injured, changes in the body of the neuron, proximal and distal segments, as well as in the site of injury will depend on the degree of injury.

Grade I injury

In mild nerve damage corresponding to grade I, there may be a temporary conduction block with partial or complete demyelination of axons at the site of injury (the nerve impulse cannot pass through the damaged area of the nerve), but the ability to restore the nerve is preserved. In this case, it is possible to fully restore the conduction and function of the nerve sometime after the injury.

Grade II injury

After the injury, changes occur both in the axon itself and in the body of the nerve cell. In the first 2 days after the injury, there is leakage of intra-axonal fluid from the ruptured axon, swelling of the distal segment increases, neurofibrils gradually disappear. In the body of the neuron, the perikaryon nucleus increases in volume and shifts to the periphery [30]. Disintegration and dissolution of Nissl bodies is observed around the nucleus, which is manifested by the loss of staining with cationic dyes. This phenomenon is referred to as "chromatolysis" or "tigrolysis". The metabolic activity of the neuron shifts towards the synthesis of structural and reparative products. Glial cells located near the neuron fill all synaptic gaps of the perikaryon, isolating it (perineuronal glial isolation). This process is probably required for the repair of the neuron. The final caliber of the axon depends largely on the restoration of the cell body and connections with the target organ [31]. Presumably, this is due to neurotrophins not receiving "neuronal food" (trophic factors) from target cells. The closer to the perikaryon the axonotomy occurs, the more likely the neuron is to die [32]. After denervation of the end organ, two ways of reinnervation can be observed: through collateral branching of intact axons or through regeneration of a damaged axon [33]. If <30% of axons are injured, the main mechanism of regeneration is collateral branching, which starts in the first 4 days after the injury and can last up to 6 months [34]. If >90% of axons are injured, recovery is possible by axon regeneration [35]. Three main processes are required for complete nerve recovery: Wallerian degeneration (cleaning of the distal end of the nerve), axon regeneration, and reinnervation of the end organs.

Wallerian degeneration is a process that begins in the area of the axon distal to the site of injury, usually 24–36 h after the trauma, and is manifested by complete fragmentation of the axon and myelin. After nerve damage, SCs become active within the first 24 hours, increasing the size of nuclei and cytoplasm. Schwann cells play an important role in the regeneration of the axon injury. If SCs are not in contact with axons, they enter a non-myelinating state, reducing the expression of some proteins [36]. This further leads to the synthesis of neurotrophic factors, such as nerve growth factor (NGF) and ciliary neurotrophic factor (CNTF) [37]. Against this background, active SC division occurs with the formation of undifferentiated daughter cells, which

can help to close the diastasis between two nerve segments. In addition, the newly formed cells initiate an inflammatory process, which is joined by endoneurial mast cells. During the first 2 weeks after the injury, they markedly proliferate, which leads to the release of histamine and serotonin, promotes capillary permeability and facilitates the migration of macrophages [38]. The latter, together with SC, phagocytose damaged axon and myelin particles. SC phagocytosis is supported by MAC-2 protein [39]. Through this process, damaged parts of the nerve are removed and the site of injury is cleared, which promotes nerve repair. Purification of decay products can last from one week to several months [40]. In the initial stages after the injury, the endoneurial sheaths are swollen, but their diameter decreases after 2 weeks. After the endoneurial sheaths are cleared of decay products, SCs join together and form chains (Büngner bands) that guide the regenerating axon to the target organ. This promotes full or partial repair of nerve function. It is known that after nerve injury, a growth cone is formed in the proximal axon stump. Calcium has been found to play an important role in this process [39,41]. Filopodia are located in the growth cone. They analyze the microenvironment and find their way to the Büngner bands. Initially, filopodia do not have a clear orientation, but subsequently gain direction due to increased expression of actin and myosin [36,41]. Due to the release of SC fibronectin and laminin, the growth cone adheres to the basal membrane of the endoneurial tube, which increases the chances of reaching the target. When passing through scar tissue, the growth cone pathway may be disrupted, so the growth cone releases proteases and plasminogen activators to clear the pathway [42].

The changes that occur in the proximal part of the nerve after its injury are complex and can vary depending on the location of the injury site relative to the neuron body and the severity of the injury. Usually, the decay of the proximal part of the nerve is limited (only up to the first Ranvier node). If the site of injury is located very close to the neuron body, apoptosis may occur. This is associated with impaired trophicity of neuron [43]. In case of severe damage to the proximal part of the nerve, the genetic program of the cell for regeneration phase is changed. After the regenerating axon reaches the target cell, gene expression of the neuron returns to a maintenance state [36]. Spontaneous recovery of the lost function occurs in most cases and lasts from several weeks to several months.

Grade III injury

In the case of damage of the III grade, a more pronounced local reaction is observed. These injuries occur within the bundles. Inflammatory changes are larger, the bundles are swollen, contain areas of hemorrhages, and the nerve fiber within the elastic endoneurium is involved. The inflammatory process results in the deposition of collagen molecules along the outer surface of the basal membrane of the SC, which disrupts the intrafascicular structure and leads to the appearance of a spindle-like shape of the injured segment. The resulting intrafascicular injury prevents axonal regeneration, causing prolonged denervation of endoneurial tubes. If the endoneurial tube has not received an axon, it is completely filled with fibrous

tissue. Restoration of the target tissue function is possible only partially, in some cases requiring surgical treatment [30, 32, 34, 39–41].

Grade IV injury

With a grade IV injury, changes occur within the subepineurial space. Due to destruction of the endoneurial and perineurial sheath and expressive inflammatory changes, targeted axon growth is impaired. Macroscopically, it appears like a spindle-shaped thickening of the nerve at the site of the injury. This is due to the fact that during movement, the regenerating axon encounters the scarred tissue and grows in different directions and planes, without being limited by sheaths [44]. In the areas of the greatest damage, nerve bundles are separated by dense fibrous tissue. Nervous tissue is represented by small groups (Büngner bands), separated from each other by endoneurial fibrosis. Fibrous thickened perineurium is observed in various areas [26, 27, 44]. The diameter of the regenerating axon is smaller than normal, and only some of these axons are myelinated. The caliber of blood vessels is increased due to intima thickening, there are areas of their obliteration. Lymphocytes are accumulated around the vessels. In the proximal and distal segments, there is significant dense collagen thickening of the epineurium above and between the nerve bundles. Given the disturbed architectonics of nerve bundles due to large inflammatory changes and destruction of the endoneurial and epineurial membranes, spontaneous regeneration and restoration of the target organ function should not be expected [45]. Only incomplete recovery is possible with surgical treatment.

Grade V injury

With a grade V injury, in addition to the changes described above, the integrity of the epineurial sheath is violated. Regenerating axons can sprout into surrounding tissues without reaching their final destination. During neurotmesis, a new tissue ("nerve bridge") is formed between the distal and proximal stumps [46]. This structure helps to regenerate the axon from the proximal to the distal segment. A.-L. Cattin et al. [46] characterized it as "a mixture of cells of inflammatory process and a matrix consisting of macrophages (50%), neutrophils (24%), fibroblasts (13%) and endothelial cells." Scientists have found that the newly created blood vessels guide the migrating cords of Schwann Cells. This multicellular process is initiated by hypoxia, which is selectively perceived by macrophages inside the bridge and through vascular endothelial growth factor (VEGF-A) secretion induces polarization of the vascular network, which reduces hypoxia [47]. SCs then use blood vessels as "pathways" to cross the bridge and guide regrowing axons. Scar tissue can obstruct the growth cone pathway, so growth cones release proteases and plasminogen activators to clear the pathway of cells and matrix that may interfere with their development. This process helps ensure effective cell-to-cell communication and optimal conditions for growth and growth cone development [41]. Successful axon regeneration also depends on neurotrophic factors that are activated during injury to the SC [48]. One such factor is the NGF-protein. This protein alters the gene expression of the neuron, which promotes its regeneration. NGF-protein on Schwann Cells receptors of Büngner bands has been found to energise

the regenerating axon [36,38]. When the growth cone reaches the endoneurial tube, it has a better chance of reaching the end organ. To attach to the basal lamina of the endoneurium, the growth cone utilises fibronectin and laminin proteins, which produce SCs [38, 48]. A maturation process (remyelination, increase in axon diameter, functional reinnervation) must occur to achieve functional connection [42,48]. The main factors affecting the efficiency of neuroregeneration in this type of injury are the length of the tear, the presence and amount of scar tissue, the accuracy of axon guidance, and the viability of end organs. Without surgical intervention, partial restoration of function is impossible.

Traction nerve injury

Traction injury of the peripheral nerve is an injury resulting from stretching of the nerve beyond its elasticity for various reasons: a fall from a height, sudden non-physiological movements during sports injuries, a road traffic accident, particularly involving a motorcyclist [49]. In the case of a closed fracture in the area of the distal metaepiphyses of the humerus or femur, displaced bone fragments can compress vessels and nerves, which is accompanied by significant stretching of their length. Cases of nerve injury with its stretching in the case of gunshot wounds or mine blast traumas have also been described [50]. In case of a gunshot injury during the passage of the bullet through the tissues, the PN can be injured due to direct mechanical action, shock waves and the formation of a temporary cavity. When such a cavity is formed, gross deformations of the surrounding tissues occur in the form of bending and stretching, which can lead to gross deformations of the neurovascular bundle adjacent wound canal zone. In the case of a mine blast trauma, the shock wave, spreading along the loose fiber between the fasciae, can tear nerve fibers and vessels, even at a considerable distance from the wound. In some cases, the nerve may remain intact externally, but there are intra-stem changes of the type of axonotmesis [49, 51].

One of the first scientists to investigate TIPN was H. Platt. He established a relationship between severe adduction injury of the knee and common peroneal nerve palsy. To describe this injury in a fundamental work published in 1928, H. Platt used the term "ligamentous peroneal nerve syndrome" [52]. With such an injury, there is severe knee adduction with rupture of the lateral capsule near the tibia, avulsion of biceps tendon, rupture of the lateral collateral ligament and both cruciate ligaments, as well as rupture of the ilio-tibial tract with severe stretching of the peroneal nerve. The above work laid the foundation for understanding the relationship between knee injury and nerve injury. B. Highet and W. Holmes began researching this pathology in 1943. They analyzed 8 clinical cases of surgical treatment with histological examination [53]. The results of the study showed that the pathological changes resulting from PNI spread to a considerable distance from the damaged area, manifesting in the form of fiber degeneration, intraneurial fibrosis, and vascular abnormalities. In addition, the examination revealed rupture of the PN sheaths of varying degrees in different parts of the nerve, as a result of which the nerve may appear intact, fusiform, or with impaired integrity

during macroscopic observation. The diameter of the axons that passed through the lesion area and reached the distal segment was predominantly small, with most axons being unmyelinated. The scientists concluded that a large nerve resection has a negative impact on the results of restoring its function. Only 1 out of 8 clinical cases achieved a satisfactory result after small peroneal nerve resection. This is because postoperative stretching of the nerve when the knee joint is extended causes the nerve to become excessively elongated, which can cause re-injury. Researchers recommend considering the location of the epineural suture and the length of the nerve resection to achieve optimal results in restoring nerve function [54].

In the article by M. Kwan et al. [55] data on the biomechanical properties of peripheral nerves, in particular on their stress-strain characteristics, stretching patterns, and changes in conduction due to stretching were presented. It was found that during stretching peripheral nerves exhibit a non-linear stress-strain behaviour with a gradually increasing low initial modulus with increasing strain until a maximum value is reached. Under the action of tension, the perineurium inside the nerve is torn, but the outer sheath of the nerve remains intact. Studies have also shown that peripheral nerves *in situ* experience significant stretch but minimal stress (<0.05 MPa), although *in situ* strain may vary with limb position. The obtained results suggest that a long-term increase in mechanical stress can negatively affect the electrophysiological properties of the nerve, since even a small stretch (by 6% of the length) of the nerve *in situ* or a strain <10% of the ultimate nerve strength results in a marked change in the conduction properties [56]. M. Mahan et al. [57] investigated the biomechanical properties of the PN during its stretching. It was found that if the PN is stretched quickly, then its biomechanical behavior is similar to that of slow stretching with the presence of three phases (elastic, inelastic and rupture). The severity of injury depends on the rate and deformation of the stretch, which is determined predominantly by the force of stretching. Thus, the direction of stretching force significantly affects injury outcomes independent of velocity, which is important for understanding clinical injury patterns. Nerves are stretched unevenly along the length, but with greater elongation in the periarticular area. The microarchitecture of nerve damage was analyzed. Using mathematical cluster analysis, the researchers identified four levels of severity of traction injuries: intact, elastic stretching, inelastic stretching, and tensile tear. Nerves stretched within the elastic norm lose their reserve, that is, the tortuous fibers straighten out and become straight, with few damaged axons. When the nerve is stretched beyond its elastic limits, axon and nerve sheath ruptures are characteristic, particularly at a considerable distance from the epicenter of pathomorphological changes. Alignment of nerve fibers has been found to be an early compensation in traction injury, which explains the elastic stretching. The accumulation of microtears in nerves after stretching is noteworthy, as this process was closely correlated with the severity of nerve injury and progression to complete rupture. The authors suggest that nerve function recovery after axonotmesis is determined by the degree of integrity of

the endoneurium, and not by other structural elements. The force of stretching and the direction of its application to the nerve trunk determine the severity of TIPN.

The results obtained are of practical importance for the development of new methods of treatment and restoration of the function of the nervous system after traumas and injuries [58,59].

Conclusions

Traumatic injuries of the PN occupy an important place in the structure of general traumatism, accompanied by a significant socio-economic effect due to frequent disability of the injured.

A feature of TIPN is a mosaic type of injury along the entire length of the nerve with areas of injury to the nervous system of varying severity, which makes it difficult to classify the available clinical picture.

Limited ideas about the mechanism and pathomorphological picture of TIPN make it impossible to develop optimal treatment tactics and promote further experimental studies of this type of injury.

Disclosure

Conflict of interest

The authors declare they have no conflict of interest and no personal financial interest in the preparation of the article.

Ethical guidelines

This article contains no studies involving humans or animals.

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