SPINAL CORD INJURY AS A TRIGGER FOR CHANGES IN THE INTESTINAL MICROBIOTA

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Objective. To analyze the peculiarities of changes in intestinal microbiota in spinal cord injury.
Material and Methods. The literature search was carried out for the period of 2012–2022 in the PubMed, ScienceDirect, eLibrary and GoogleScholar databases for the following keywords: spinal cord injury, microbiota, and dysbacteriosis. Out of 220 literature sources, 40 full-text articles were selected which analyze the influence of spinal cord injury on the state of the intestinal microbiota using an innovative method of metagenomic high-throughput 16S sequencing.
Results. Literature data on the pathogenesis of organ dysfunction in spinal cord injury, as well as its impact on the state of the intestinal microbiota are presented. The results of experimental and clinical studies of the intestinal microbiota in spinal cord injury and its influence on the development and course of the pathological condition are reported.
Conclusion. Understanding how the intestinal microbiota changes after spinal cord injury and what role it plays in potentiating inflammation or protecting the spinal cord from secondary injury and infections is very important in determining the strategy and tactics for managing patients. Possession of methods for correcting intestinal microbiota disorders in SCI is important in the treatment of such patients.
Key Words: spinal cord injury, microbiota, dysbacteriosis.
Please cite this paper as: *Ivanova EYu, Kirilina SI, Sirota VS, Gusev AF. Spinal cord injury as a trigger for changes in the intestinal microbiota. Hir. Pozvonoc. 2023;20(2):49–56. In Russian.*
DOI: http://dx.doi.org/10.14531/ss2023.2.49-56.

The frequency of spinal cord injury (SCI) is about 10.4–57.8 cases per million in developed countries and 12.7–29.7 cases per million in developing countries. A total of 0.9 million cases of common SCI were registered around the world in 2019. The incidence rate is 12 per 100 thousand people. SCI is more common in men (79.8 %) than in women (20.2 %). Among the main reasons are car accidents (38 %) and falls from heights (31 %). As for patients suffering from spinal cord injury, there are two peaks in the age distribution: the first one manifests itself at the age of 15–29 years, and the second one – after 55 years old. SCI prevails in the cervical spine and accounts for more than 50 % of all spinal cord injuries. In comparison with SCI at the lower levels, an injury of the cervical spine (CS) results in a more severe degree of disability [1].

The level and volume of the spinal cord injury have the greatest influence on the functional outcomes of SCI. The effect of SCI on the loss of motor and non-motor functions depends on the localization of the injury. Nerves controlled by segments of the spinal cord below the injury site often lose their connections, and therefore the connection between the body and the brain through the descending motor pathways and ascending sensory pathways is disrupted. SCI, in addition to impairments of sensation and voluntary movement, changes the functioning of the autonomic nervous system, resulting in dysfunction or insufficiency of numerous organs due to the spinal cord vital involvement in the coordination of body processes. Any injury to the spinal cord disrupts sympathetic innervation, while the function of the parasympathetic division is preserved.

The imbalance in the functioning of the sympathetic and parasympathetic nervous systems caused by SCI results in dysregulation of the cardiovascular system and the onset of vasoplegia, which leads to arterial hypotension, neurogenic shock, and bradycardia. Neurogenic shock is most clinically significant at neurological levels of injury above T6, because these injuries prevent the transmission of central impulses in the middle part of the thoracic spinal cord where sympathetic nerves exit, which are important in maintaining vascular tone [2].

In the acute stage of traumatic injury of the CS, 84 % of patients with injury at the level of C1–C4 and 60 % of patients with injury at the level of C5–C8 have respiratory complications [3]. Respiratory complications caused by variable paralysis of inspiratory and/or expiratory muscles, as well as intercostal muscles with injuries above T11, paralysis of the diaphragm with injuries above C5, weakness of the abdominal muscles with injuries above L1, as well as excessive secretion of viscous bronchial mucus and difficulty in coughing it up due to muscle weakness, are among the leading causes of respiratory failure and even mortality after cervical spinal cord injury. However, the fact that individuals with lower thoracic SCI acquire respiratory dysfunction implies that the processes involved in the development of SCI-related respiratory difficulties are ambiguous [2, 4].

SCI causes systemic inflammatory reactions characterized by increased circulation of immune cells and proinflammatory mediators, resulting in infiltration of internal organs by inflammatory

cells and retention of the inflammatory microenvironment that contributes to organ dysfunction [5].

The literature also describes the SCI-induced immune depression syndrome (immune paralysis, SCI-IDS), the primary cause of which is the loss of innervation of secondary lymphoid organs such as the spleen that can increase susceptibility to infections (such as urinary tract infections and pneumonia) [6].

SCI can disrupt supraspinal control of the bladder and result in a neurogenic bladder characterized by dysfunction in its filling and emptying. Correspondingly, patients with SCI have an increased risk of urinary tract infections and renal injury, which lead to the onset of acute or chronic renal disease [2].

In SCI, changes occur in the digestive system due to disruption of the functioning of the enteral nervous system due to autonomic dysfunction. Sympathetic preganglionic neurons that control the small and large intestines are mostly found in the thoracic segments of the spinal cord, from T5 to T10 [7]. Consequently, most of the control of the brain and stem over the spinal autonomic system innervating the intestine is lost when a spinal cord injury occurs at the T5 level or higher. The lack of normal sympathetic regulation in the small and large intestine disrupts intestinal motility, mucosal delivery, vascular tone, and immune function [8]. The gastrointestinal tract (GI tract) hypoperfusion associated with hypotension in neurogenic shock is of special concern, as the gastrointestinal tissues are deprived of oxygen required to maintain the luminate barrier integrity. Since one of the main functions of a healthy intestine is the absorption of nutrients, changes in the nutritional status of patients can be identified in the presence of motor evacuation disorders of the intestine [9, 10].

The loss or disruption of one or more gastrointestinal tract functions after SCI may result in an ecological imbalance of microorganisms in the intestine, called dysbacteriosis [11]. Indeed, persistent changes in the bacterial composition of the intestine have been described in numerous clinical and preclinical studies of SCI [12–17].

The objective is to analyze the features of changes in the clinical microbiota in SCI according to the literature sources.

Material and Methods

Design: a systematic review of the literature. The literature search was carried out for the period of 2012–2022 in the PubMed, ScienceDirect, eLibrary, and Google Scholar databases for the following keywords: spinal cord injury, microbiota, and dysbacteriosis. A total of 220 literature sources were found. We used only full-text articles. A total of 40 full-text articles were selected that analyze the influence of spinal cord injury on the state of the intestinal microbiota using an innovative technique of metagenomic high-throughput 16S sequencing.

Results

Intestinal microbiota (general information)

To evaluate the role of the intestinal microbiota in critical conditions, one of which is the SCI of CS, academic and practical knowledge is required regarding the normal functioning of the intestinal microbiota, its effect on metabolism and intestinal epithelium, as well as an assessment of its part in the development of complications in critical conditions.

The gastrointestinal tract contains more than 100 trillion microbes. The set of genes in the intestinal microbiota (intestinal microbiome) is estimated at about 3 million, which is 150 times more than in the human genome. The growth and composition of the intestinal microbiota are affected by many factors, including immune mechanisms, dietary factors, and intestinal motility. Each part of the body is a highly specialized niche characterized by its own microbial consortia, community dynamics, and interaction with host tissues [18].

The gastrointestinal tract is one of the most complex micro-ecological invironment of the human body, in which the total area of the mucous membrane, amounting to about 400 m^2, has an exceptionally high and diverse environment (over 1,000 species of heterogeneous bacteria, viruses, archaea, and fungi). Bacteria account for 35 to 50 % of the volume of the contents of the large intestine of an individual. An increase in the density of microorganisms and the biological diversity of species is observed along the gastrointestinal tract in the caudal-cervical direction. The microbial inhabitants of the intestine differ from one person to another. Nevertheless, metagenomic high-throughput sequencing identified the reliable presence of 12 bacterial types, as well as a fungal-rich community. The main bacterial types are *Firmicutes* (most of them belong to the *Clostridia* class, including butyrate-producing species) and *Bacteroidetes* (65 characteristic phylotypes). They are followed by *Protobacteria, Actinobacteria, Fusobacteria*, and a smaller number of *Verrucomicrobia* [19].

There are differences in the composition of the intestinal microbiota between the intestinal lumen and the surface of the intestinal mucosa. The cavity microbiota is more changeable and does not interact with the mucous membrane. Its composition depends on the rate of movement of food substrates through the alimentary tract, especially dietary fibers, which are nutritious materials and act as a matrix on which colonies of intestinal bacteria are fixed and formed. The mucosal (crypt-associated) microbiome interacts with the gastrointestinal mucosa, forming a microbial-tissue complex: microcolonies of bacteria and their metabolites, epithelial cells, goblet cells mucin, fibroblasts, immune cells of Peyer's patches, phagocytes, white blood cells, lymphocytes, and neuroendocrine cells [20].

Microbiota functions and its composition in SCI

The intestinal microbiota protects the microorganism from colonization by pathogens, regulates intestinal permeability, boosts the immune system, synthesizes essential vitamins, and produces secondary bile acids [21].

The activity and influence of the intestinal microbiota are not limited to

local immune-intestinal interactions but spread through major communication axes to distant organs, including the brain. Intestinal microbes are core components of a bidirectional communication system between the central nervous system (CNS) and the digestive system, the "intestine-brain" axis. The intestinal microbiota can connect to the brain through several pathways, including neural and non-neural ones. The brain regulates the intestinal microbiota through neuronal pathways (for example, the autonomic and enteric nervous systems), the hypothalamic-pituitary-adrenal axis, etc. Neuronal pathways release neurotransmitters to modulate intestinal motility, permeability of the intestinal barrier, fluid retention, the activation of resident immune cells, and the composition of the intestinal microbiota. The released cortisol contributes to the regulation of intestinal homeostasis [22]. Intestinal microbes produce various neuroactive metabolites or precursor molecules (for example, tryptophan), which are essential for the synthesis of serotonin, dopamine, gamma-aminobutyric acid, acetylcholine, and melatonin. These neuroactive metabolites transmit signals to the central nervous system through the afferents of the vagus nerve or directly from the bloodstream into the nervous parenchyma through the hematoencephalitic barrier [23]. Intestinal microbes also interact with the central nervous system through their influence on adaptive and innate immunity, affecting the immune system, which likewise has a two-way connection with the central nervous system [24].

Chu et al. [25] have demonstrated that intestinal microbes are essential for the normal development, functioning, and recovery of the central nervous system after injury, as well as for the regulation of nervous activity and host behavior in response to environmental signals.

One of the major functions of the intestinal microbiota is its ability to breakdown indigestible polysaccharides, synthesising short-chain fatty acids (SCFA), which provide colonocytes with metabolic fuel. The main representatives of bacteria fermenting carbohydrates in the intestine are bacteria of the genera *Firmicutes* and *Bacteroides*. Acetate, propionate, and butyrate are among the synthesised SCFA [26].

Butyrate is the most relevant SCFA, with a modulating effect on the growth and differentiation of epithelial cells and cells of the immune system. It has a strong anti-inflammatory impact on the resident macrophages of the central nervous system and may suppress the ongoing inflammation in it [27]. Low levels of butyrate have influence on long-term recovery after SCI [12]. In studies of the intestinal microbiome in patients in critical condition, butyrate-producing bacteria are rare or absent at all, while the production of butyrate is minimal [28]. The pathophysiological consequences of this condition are predictable: the death of intestinal epithelial cells, a dysfunction of intestinal barrier, and unregulated inflammation.

What is the pathogenesis of a disruption of the bacterial community's homeostasis in critical conditions? The intestine is a target organ for many different types of stress, due to sepsis, shock, burns, injury, and infection. Considering that SCI is a stressful factor resulting in intestinal dysfunction, this can lead to a considerable change in the composition of the intestinal microbiome [12]. The main technique for eliminating microbes from the intestine in healthy people is a transit through and out of the gastrointestinal tract, which usually happens quickly. A healthy adult with defecation secretes about 1014 bacterial cells per day [21]. In the stomach, which usually empties quickly and has an extremely high acidity, the transit time also slows down, and the pH is neutralized by using medicines to suppress the production of hydrochloric acid [29].

Other systems of microbial elimination are also affected during critical conditions: bile salt synthesis declines, IgA production is interrupted and the dense mucosal barrier of secreted antimicrobial peptides is lost. The final effect is to decrease the elimination of bacteria, especially in the upper gastrointestinal tract, which becomes a reservoir with a neutral pH and rapidly overgrown with gram-negative bacteria [21].

Hypoperfusion with a decrease in systemic blood pressure and intestinal wall reperfusion causes significant inflammation of the mucous membrane, leading to a chain of disorders. An elevated nitrate level and an altered oxygen gradient in the mucous membrane cause the growth of *Proteobacteria* type microbes, which include such gram-negative rods as *Pseudomonas aeruginosa* and *Escherichia coli*, as well as some representatives of the *Firmicutes* type: *Staphylococcus aureus* and *Enterococcus spp.* [31].

The world literature shows that in recent years, with the help of metagenomic high-throughput sequencing, studies of the intestinal microbiome in SCI have been performed.

Until now, clinical studies have mainly been limited to data collected during the treatment and rehabilitation of patients with chronic forms of traumatic spinal cord disease, and only one study was performed on patients in the acute injury period [12].

The first report on changes in the intestinal microbiome of patients suffering from spinal cord injury showed a specific reduction in the number of beneficial microbes from the genus *Firmicutes* producing butyrate after 12 months or more after injury in comparison with healthy people in the control group. It has been proposed that decreased butyrate levels may contribute to microglia-mediated neurotoxicity in patients with SCI, which affects long-term recovery after injury. It is worth pointing out that glial cells are known to enhance hypersensitivity to pain by releasing signaling molecules (multiple proinflammatory cytokines). Considering neurotoxicity, which intensifies the sensation of pain, a reduced level of butyrate may be a permanent trigger factor for neurogenic pain [12].

In a cohort study, Zhang et al. [14] observed an increase in *Proteobacteria* and *Verrucomicrobia* and a decrease in *Bacteroidaceae* and *Bacteroides* in patients with chronic SCI. A total of 43 male patients with chronic SCI (20 with quadriplegia and 23 with para-

plegia) and a comparison group of 23 healthy adult men were included in the analysis. It has been established that the overall diversity of the intestinal microbiota is considerably reduced in 6 months after SCI compared with healthy people in the control group. Among the spectrum of changes in bacterial types and genera and the overall reduction in microbial diversity after SCI, the authors discovered that *Bacteroides* (a genus of the order Bacteriodales) increased with SCI. They also noticed an increase in the number of bacteria from *Proteobacteria* and the *Verrucomicrobia* type. These changes were directly correlated with aspects of neurogenic intestinal dysfunction as well as with the degree of neurologic impairment, which revealed more specific microbial changes [14].

In the next study conducted by the same group of researchers [15], the established changes in the microbial profile of patients with SCI were compared with the profiles of lipids in their serum.

Lin et al. [32] also analyzed the microbiota composition of 46 people (23 patients with SCI and 23 healthy ones) and reported that the content of *Parabacteroides*, *Alistipes, Phascolarctobacterium, Christensenella, Barnesiella, Holdemania, Eggerthella, Intestinimonas, Gordonibacter, Bilophila, Flavonifractor*, and *Coprobacillus* was higher in patients with spinal cord injury.

Yu et al. [33] found that the composition of the intestinal microbiota in patients with SCI differed from that of healthy people (n = 24) in a case-control study of 45 patients with complete and incomplete thoracic spinal injuries. As for the group with complete SCI at the thoracic level, it showed a greater deviation in microbial composition than the group with incomplete injury, compared with healthy people.

A large population of patients in the acute phase after injury and healthy people of the same age and gender participated in a study performed in 2021 by Bazzocchi et al. [34]. The researchers discovered that potentially pathogenic, proinflammatory, and mucus-decomposing bacteria increased the intestinal microbiota of SCI patients, whereas SCFA producers dropped. In addition, dysbacteriosis of the intestinal microbiome was closely associated with the severity of the lesion after SCI [34].

More numerous are the studies of the intestinal microbiome in experimental animals that also confirm its specific changes after spinal cord injury. Kigerl et al. [8] discovered that in a model of mice with SCI and concussion at the T9 level, mice demonstrated decrease in *Bacteroidales* bacteria and increase in *Clostridiales* bacteria. This study showed that the introduction of probiotics with lactic acid producing bacteria resulted in neuroprotection and better restoration of neurological functions.

In a rat model of thoracic SCI, O'Connor et al. [16] proved a change in the composition of the intestinal microbiota due to an increased content of intestinal *Lactobacillus, Clostridium disporicum*, and *Bifidobacterium choerinum* and a reduced level of *Clostridium saccharogumia*.

In an experimental study by Myers et al. [13], intestinal microbiota dysbacteriosis was noted in mice with SCI at the T9 level, characterized by the spread of *Bacteroidetes* and a decrease in *Firmicutes* [13]. The difference in outcomes may be caused by an experimental deviation.

Du et al. [35] used metagenomic analysis with genome and gene resolution to investigate the dysbacteriosis of the intestinal microbiota following experimental SCI at the T4 and T10 levels. The results showed that the number of beneficial commensals (*Lactobacillus johnsonii* and *CAG-1031 spp.*) reduced significantly while potentially pathogenic bacteria (*Weissellacibaria, Lactococcuslactis A*, and *Bacteroidesthetaiotaomicron*) rose after injury. Functionally, the biosynthesis of tryptophan, vitamin B6, and folic acid encoded by microbial genes decreased in fecal matter after SCI [35].

According to a model of Yucatan miniature pigs with bruised compression from SCI in T2 or T10, Doelman et al. [36] identified changes in the intestinal microbiome's dynamics after SCI and defined the acute stage (0–14 days after injury) as a special period of time when many bacterial fluctuations occur before returning to baseline levels.

SCI promotes intestinal permeability and bacterial translocation associated with the activation of immune cells in intestinal lymphoid tissue by increasing the population of B cells, $CD8^+$ T cells, dendritic cells, and macrophages and lowering the number of $CD4^+$ T cells. There were attempts at therapeutic effects on the intestinal microbiome in experimental studies. In mice with SCI who were prescribed probiotics (VSL#3), neurological impairment was reduced, recovery of the musculoskeletal system improved and the anti-inflammatory response was boosted by an increase in the number of T cells in the intestinal lymphoid tissue [8].

Moreover, the integrity of the intestinal barrier and functional recovery improved in mice with SCI treated daily with melatonin due to a reduced number of *Clostridiales* and an increased number of *Lactobacillales* and *Lactobacillus*, which was associated with a more favorable cytokine profile [37]. It has also been proven that lactic acid supplements improve functional recovery after spinal cord injury [8].

There have been attempts to transplant fecal microbiota into experimental animals with SCI. In these studies, it was proven that fecal microbiota transplantation prevented dysbacteriosis associated with SCI, even improved motor function, and reduced cases of anxiety-related behaviour [38]. Fecal microbiota transplant may enhance the number of fecal SCFA and inhibit the transmission of IL-1 and NF-kB signals in the spinal cord and the transmission of NF-kB signals in the intestine after SCI [38]. A recent study also reported that minocycline treatment reduced anxiety behaviour associated with SCI and systemic inflammatory response by altering the *Firmicutes/Bacteroidetes* ratio [39].

Conclusion

The study of the role of the intestinal microbiota in acute injury to the central nervous system is one of the

most innovative studies in clinical and experimental medicine. It is clear that patients who have undergone SCI are exposed to a variety of other stressful factors, including enteral nutrition, surgical treatment, antibiotics, and the use of a large number of other medicines that negatively influence the composition of the intestinal microbiota. However, experimental models in which it is possible to limit these confounding variables also note a significant impact of trauma on the microbiota composition. An understanding of how the intestinal microbiome changes after SCI and its role in potentiating inflammation or protecting the spinal cord from secondary injury and infections is extremely essential for defining strategies and tactics for the management of patients with SCI. Knowledge of correction techniques for disorders of the intestinal microbiota in SCI can become an indispensable tool in the treatment of patients. To address this issue, longitudinal investigations in individuals with acute SCI during the first weeks following injury with a prospective evaluation of the microbiota composition and functional characteristics are required. This will provide an option to compare certain groups of bacteria with such indicators of outcomes as sensorimotor recovery or neuropathic pain and, in the future, use the microbiome as a prognostic biomarker of recovery after neurological disorders, similar to the dysbiosis index in stroke [40].

The study had no sponsors.
The authors declare that they have no conflict of interest.
The study was approved by the local ethics committee of the institution.
All authors contributed significantly to the research and preparation of the article, read and approved the final version before publication.

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Received 30.01.2023
Review completed 05.04.2023
Passed for printing 14.04.2023

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