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Review

Recent therapeutic approaches for spinal cord injury

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ABSTRACT

Spinal cord injuries refer to the impairment of motor and sensory functions due to traumatic or non-traumatic damage to the spinal cord, which plays a crucial role in the central nervous system. In traumatic cases, an examination is conducted to distinguish between 'primary injury' resulting from the impact and 'secondary injury' involving biochemical events. In non-traumatic cases, physiological or neurological conditions are considered. Spinal cord injuries cause damage to the white and gray matter located in the deeper parts of the spinal cord. To classify the various complications caused by this damage, a fundamental treatment scale known as the International Standards for Neurological Classification of Spinal Cord Injury, established by the American Spinal Injury Association, has been created to facilitate diagnosis and treatment. The course of the disease is better understood through sensory and motor tests conducted according to this standard. Complications in the lesion area are often diagnosed using magnetic resonance imaging. This review addresses the structure of the spinal cord, the causes and factors of injury, and some current clinical approaches and treatment methods.

Keywords: American Spinal Injury Association, gray matter, magnetic resonance imaging, primary injury, secondary injury, spinal cord.

The spinal cord is a nervous tissue that provides the connection between the brain and the organs, carries signals to the brain, and thus plays an important role in the central nervous system (CNS) by controlling reflexes and certain movements. Essentially, it is the main nerve cord responsible for signal transmission. Spinal cord injury (SCI) is identified through neurological assessments and sensory tests, and as a result of these injuries, patients experience loss of autonomic movements and functions.[1]

The oldest accessible document on SCI that is considered a reference is the Edwin Smith Surgical Papyrus, which is believed to have been authored by Imhotep, and known for various scientific studies during Ancient Egypt.[2] This historical document systematically discusses bodily injuries. Cases are numbered, and for each case, a specific prognosis and treatments applicable under the conditions of that period are suggested.[3] Subsequently, many scientists, including Hippocrates, the Roman Aulus Cornelius Celsus, Galen of Pergamon, and Paul of Aegina, studied and documented SCIs according to the conditions of their respective periods.[1-3]

Today, SCI is primarily categorized into traumatic and non-traumatic injuries. It manifests through complications and distinct symptoms that arise based on the progression of the condition.[4] Various treatment methods and clinical studies are implemented based on these complications.

SPINAL CORD

The medulla spinalis (spinal cord), a gently curved, cylindrical-shaped nervous tissue located within the vertebral canal, varies in structure among most vertebrate animals.[5] There are seven nerve roots within the cervical vertebrae, and they are named according to their respective vertebrae (C1-C7). The longest segment is the thoracic spine, which contains 12 nerve roots (thoracic vertebrae). The lumbar

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vertebrae consist of five distinct nerve roots (lumbar vertebrae, L1-L5). The sacrum is made up of five sacral nerve roots, while the coccyx (tailbone) contains four nerve roots. The terminal point of the spinal cord is called the conus medullaris.[6] The medulla spinalis extends from the brainstem to the conus medullaris. One of the key functions of the vertebral canal is to provide an open and protective space for the spinal cord to pass from the cranium to the sacrum.[7]

The medulla spinalis is composed of gray and white matter. The inner gray matter contains nuclei, which include the cell bodies, dendrites, and originating axons of the brain hemispheres. The outer white matter consists of blood vessels, myelinated fibers, and basal ganglia.[1] The disruption of the basal ganglia network leads to various movement disorders.[8]

Basal ganglia can essentially be divided into three categories: input nuclei, output nuclei, and intrinsic nuclei. The nucleus accumbens (Acb), caudate nucleus (CN), and putamen (Put) are considered input nuclei, receiving information primarily from cortical, thalamic, and nigral sources. The output nuclei consist of the internal segment of the globus pallidus and the substantia nigra pars reticulata. One of their functions is to send basal ganglia information to the thalamus. Finally, cortical and thalamic information goes to the striatum (CN, Put, and Acb) for further processing within the basal ganglia system.[7,8]

The spinal cord is part of the CNS and facilitates the transmission of neural signals from the brain to the peripheral nervous system. This transmission mostly occurs through spinal interneurons located in the gray matter. Sensory axons in the white matter and spinal interneurons, primarily found in the gray matter, conduct and control these signals. Any damage to the spinal cord components or the disruption of axons in the passing nerves affects sensory transmission, motor signal transmission, and the autonomic nervous system at the lesion sites. This leads to motor and sensory function loss, with symptoms such as coordination loss, pain, and paralysis. Such clinical impairments are associated with axon or neuron degeneration.[6-10]

Etiology and epidemiology

The incidence, prevalence, and even gender distribution ratios of SCI vary across different regions of the world. Spinal cord injury results in permanent damage, typically caused by sudden and severe trauma, such as motor vehicle accidents, falls from heights, workplace accidents, recreational injuries, sports accidents (diving into shallow water, jumping), and, to a lesser extent, falls and injuries at home.[9-11] In studies conducted in past years, the rate of SCI due to motor vehicle accidents is higher in developing countries compared to developed countries. The primary reasons for the lower rate of traumatic spinal injuries in developed countries compared to low and middle-income countries include factors such as vehicle quality, seat belt usage, and airbags.[12,13] The global incidence of traumatic spinal injury, which is very serious and often fatal, is approximately 10.5 cases per 100,000 people.[14]

The rates of non-traumatic SCI are lower compared to traumatic injuries, and consequently, there are fewer studies related to non-traumatic SCI.[15] Causes of non-traumatic SCI include spinal tumors, transverse myelitis, spinal cord infections, neurological disorders, paraplegia, and even herniated discs.[16,17]

Pathophysiological process

When seeking appropriate treatment after this type of injury, the injury process and how it progresses are considered. In traumatic injuries, an initial mechanical damage occurs, referred to as primary injury. This is essentially the first observed problem in the patient.[18,19] In this process, where the central and peripheral nervous systems are directly affected, fractures occur, blood vessels are damaged, and neural cell structures are disrupted, transmission problems, particularly in the gray matter, arise within minutes.[19-21]

Following the mechanical damage, which is considered the first stage of the injury, the biochemical transmission system begins.[19] This is referred to as secondary damage. In secondary damage, neurotransmitters involved in the neural transmission of the injury, along with stress factors, are released from cells that have been affected, damaged, or severely injured as a result of the primary damage.[21-23] In this situation, particularly in damaged cells, free radicals, proteases, arachidonic acid metabolites, and excitotoxins such as glutamate and aspartate emerge.[24] The sudden release of neurotransmitters and these various metabolites affects cellular stability. When there is an abnormal change in the amount of glutamate in the damaged area, the internal balances within the cells are disrupted accordingly.[25] When the amount of glutamate increases excessively, it leads to the influx of calcium (Ca^{2+}) into the cell. This is a neurotoxic condition because excessive glutamate causes the death of other neurons. Neuroprotective agents prevent this potential neural damage by blocking Ca^{2+} entry, acting as channel blockers. Potassium (K+) ions also play a crucial role in the CNS, similar to Ca^{2+}.[24,26-28] Increased extracellular K+ levels, the influx of Ca^{2+} into the intracellular space, elevated tissue sodium (Na) levels, and lipid hydrolysis are among the potential secondary pathological damages that occur.[24,25,28,29]

Diagnosis

In SCI, damage is more commonly observed in the cervical vertebrae region. The junction of the thoracic and lumbar regions has a lower incidence of damage compared to the cervical region. However, when examining such traumatic accidents, it is evident that these two regions are most commonly affected, even though their frequencies may vary. Fractures and dislocations are frequently observed in SCI.[1]

Neurological examination, including sensory and motor control assessments, is conducted according to the American Spinal Injury Association (ASIA) and International Standards for Neurological Classification of Spinal Cord Injury standards, which facilitate the classification of SCIs and motor disorders. The sensory examination involves testing the areas with diminished sensation and progressing toward normal regions using a pinprick sensation test. Sensory testing is evaluated based on the impairment scale defined by ASIA.[30]

In addition to these sensory tests, magnetic resonance imaging (MRI) is commonly used to analyze different brain structures, identify lesions, and plan surgeries. Clinical research has shown that spinal cord segmentation is not as advanced as brain segmentation. However, in the past decade, significant progress has been made in the field of spinal cord MRI segmentation.[31]

The MRI examinations, such as T1, T2, diffusion, apparent diffusion coefficient, and short tau inversion recovery, are used for various purposes including assessing the severity of symptoms, investigating the structural and functional integrity of the spinal cord, determining the degree of tissue damage, and measuring morphometric changes.[32] These various MRI modalities are also used to identify gray and white matter and to measure atrophy of the gray matter.[33,34]

There is no single method that provides detailed imaging of the spinal cord and its underlying structures in cases of spinal cord deformation, abnormal densities, or contrast loss. In such situations, combinations of different approaches are used as support. For example, cross-sectional area measurement, a quantitative method, helps therapeutically evaluate disease progression. However, due to its ability to better assess microstructural damage, non-invasive nature, and sensitivity to parenchymal tissue, MRI is recommended as one of the best methods for these purposes.[31-33,34]

CLINICAL SYNDROMES

Central cord syndrome

This syndrome is the most common form of traumatic SCI. Due to severe pressure toward the center of the spinal cord following the injury, there is a slowdown in blood flow to the area, resulting in significant damage to the gray matter at the center. This condition is characterized by disproportionate sensory and muscle loss in the upper extremities compared to the lower extremities, impaired motor function, and loss of bladder control.[34,35]

Brown-Séquard syndrome

It is a neurological condition resulting from hemisection of the spinal cord. It is characterized by weakness, paralysis, and proprioceptive deficits on the same side as the lesion, with loss of pain and temperature sensation on the contralateral side.[36]

Anterior Cord syndrome

This syndrome typically affects most of the anterior portion of the spinal cord.

It characteristically results in a loss of motor function below the level of the lesion, often accompanied by loss of sensation, pain, and temperature perception. Other findings may include back pain or hypotension, autonomic dysfunction such as neurogenic bowel or bladder issues, and sexual dysfunction.[37]

Posterior Cord syndrome

This syndrome is the least common type among spinal cord syndromes. It is characterized by selective dysfunction of the posterior columns of the spinal cord. Due to the loss of proprioception, it causes impairments in movement and balance, resulting in difficulties with coordination and stability.[38]

Conus Medullaris syndrome

It is known that the spinal cord extends from the brainstem to the conus medullaris. The conus medullaris is the terminal point of the spinal cord, corresponding to the L1 segment. Injuries occurring in the T11-T12-L1-L2 regions affect the level of the conus medullaris. As a result of damage, ischemia, weakness in the legs, muscle atrophy, sensory loss, and sphincter muscle damage occur, leading to urinary and fecal incontinence and loss of reflexes.[39,40]

Cauda Equina syndrome

The cauda equina is a group of nerve roots extending below the L1 segment, known as the conus medullaris. It results from compression or damage to these nerves. The damage can affect the conus medullaris and may extend to more distant regions. It includes the axons of nerves responsible for motor and sensory transmission to the legs, bladder, anus, and perineum. Consequently, the resulting damage can cause similar symptoms to those seen in conus medullaris syndrome, including motor and sensory dysfunction in the lower extremities, bladder and bowel dysfunction, sexual dysfunction, and pain radiating to the legs and back.[40]

Syringomyelia

It is a condition characterized by the accumulation of cerebrospinal fluid within the central part of the spinal cord, leading to an increase in the spinal cord's diameter. The syringomyelic cord is highly sensitive and fragile, and its expansion can cause damage. This results in various dysfunctions, including muscle weakness, pain, and loss of reflexes and control in both the upper and lower extremities.[41,42]

TREATMENT AND CLINICAL STUDIES

Spinal cord injuries are classified in two ways to facilitate the choice of treatment, based on their type and progression:

Tetraplegia, also known as quadriplegia, refers to a condition where neural elements within the spinal cord are damaged, resulting in a reduction or complete loss of motor and sensory functions in the trunk, arms, legs, and pelvic regions, including the bladder, rectum, and uterus. In short, the term signifies paralysis affecting all four limbs.[43]

Paraplegia is a term frequently used in cases of cauda equina and conus medullaris injuries. It refers to the preservation of arm functions while causing motor and sensory loss in the lower extremities, specifically the legs and lower back, depending on the severity of the injury.[43]

After clinically assessing the patient's condition and conducting sensory examinations, physiotherapy and rehabilitation treatments are carried out. Depending on the severity of the condition, there are early and late-stage interventions. Early-stage treatment focuses on strengthening muscle functions, minimizing secondary damage complications, and providing psychotherapy when the neurological damage is less severe. Late-stage treatment aims to restore mobility function if the patient is in a wheelchair or bed, support with assistive devices, and provide medical support to help the patient achieve greater functional independence.[30-43]

Some of the clinical studies aimed at treatment for SCIs can be listed as follows:

1. It was mentioned that when the spinal cord is damaged, the axons of the nerves in that area are disrupted. Interventions aimed at increasing the number of axons in the damaged region or enhancing the speed of weak stimuli from the axons can be effective in treatment.[44]

2. Hyperbaric oxygen therapy has been observed to positively affect the biochemical transmission system. Developments have indicated that it reduces cytotoxicity, increases certain antioxidants in the spinal cord, enhances angiogenesis to improve blood circulation, and raises oxygen levels in damaged tissues.[45]

3. The use of edaravone, which acts as a free radical scavenger, has been shown to clean antioxidants and lipid peroxides and stimulate the release of interleukin-10, which functions as an anti-inflammatory agent. Studies have demonstrated that edaravone administration helps protect remaining motor neurons and prevents the progression of the disease.[46]

4. The entry of Ca^{2+} into cells, caused by increased glutamate levels, leads to toxic neuronal death. It has been observed that the administration of nimodipine, which blocks Ca^{2+} channels, can promote neurological recovery when tested with various combinations.[18]

5. Prevention of reactive oxygen species (ROS) within cells has shown promising results in the treatment of neurological disorders. Research indicates that using casuarinin significantly reduces intracellular ROS levels and glutamate-induced cell death. This finding underscores the potential of casuarinin as a therapeutic agent in mitigating oxidative stress and neuronal damage associated with SCIs and other neurological conditions.[47]

6. Various clinical studies focus on neural regeneration through stem cell research, biomaterial grafts, and filling of lesion cavities. These approaches aim to promote recovery and repair by stimulating neural regeneration and addressing damaged areas within the spinal cord.[48]

7. Recently, robotic therapy approaches have been actively used in both early and late-stage treatments. The use of hybrid assistive limb has been associated with positive outcomes, including increased endurance, improved walking speed, beneficial changes in muscle activity, and enhanced management of bladder and bowel functions.[49]

Studies have demonstrated that examinations conducted within 72 hours after a traumatic injury provide more reliable prognostic information.[50]

In conclusion, the structure of the spinal cord and the CNS more accurately reflects the extent of dysfunction resulting from damage. The preservation of the sacral sensation particularly the pinprick sensation during the early stages also offers hope for the effectiveness of potential treatments. Research at the molecular biology level, which is linked to various disciplines such as medicine, physiology, and anatomy, aims to develop diverse treatment methods by integrating with other scientific fields. This research seeks to restore lost motor functions to patients and help them return to independent daily living.

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