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Revision

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Pathophysiology of spinal trauma

Fisiopatología del trauma raquimedular

Abstract

Spinal trauma (TRM) includes traumatic lesions characterized by fractures of the spine and may also have deficits in motor and / or sensory functions due to complete or partial involvement of the spinal cord. Pathophysiologically, it occurs by two mechanisms: primary spinal cord injury and secondary spinal cord injury; The first involves the initial mechanical injury due to local deformation and energy transformation, while the second involves a cascade of biochemical and cellular processes. The evolution of these processes has been divided into 5 phases: Immediate, Acute, Subacute, Intermediate and Chronic; The study of these phases is important because it allows the selection of interventions that may possibly improve the patient's neurological prognosis.

Resumen

El Trauma Raquimedular (TRM) engloba las lesiones de origen traumático que se caracterizan por fracturas de la columna vertebral y pueden tener también déficits de las funciones motoras y/ o sensoriales por la afectación completa o parcial de la medula espinal. Fisiopatológicamente, se produce por dos mecanismos: lesión medular primaria y lesión medular secundaria; la primera implica en la lesión mecánica inicial debido a la deformación local y la transformación de energía, mientras que la segunda abarca una cascada de procesos bioquímicos y celulares. La evolución de estos procesos se ha dividido en 5 fases: Inmediata, Aguda, Subaguda, Intermedia y Crónica. El estudio de esas fases es importante pues permite la selección de las intervenciones que pueden posiblemente mejorar el pronóstico neurológico del paciente.

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Introduction

Descriptions of traumatic injury to the spine and its treatment were reported between 3000-2500 BC on a parchment written by Edwin Smith, who mentioned 48 cases of traumatic lesions affecting the Central Nervous System (CNS), of which 12.5% corresponded to spinal injuries. Writings by Hippocrates were later found, reporting traumatic and non-traumatic lesions of the spine. And in the second century AD, Galen was among the first to experiment with animals and report the changes observed by affecting a part of the spinal cord.¹

Spinal Cord Injuries (SCI) include injuries of traumatic origin affecting the bony, cartilaginous, muscular, vascular, meningeal, radicular, and medullary structures of the spine -in a joint or isolated way- at any of its levels.¹⁻³ Medullary Lesions (ML) are a devastating neurological problem characterized by the deficit of motor, sensory, and anatomical functions due to a complete or partial involvement of the spinal cord, mainly caused by trauma, occurring in about 15 to 25% of SCI.^{4,5}

SCI present mainly due to traffic or work accidents, accompanied by multiple traumatic injuries such as cranial, thoracic and pelvic. Additionally, they can also be related to injuries by firearm, falling from heights, and by an explosion, among others.¹ This medullary traumatic pathology affects mostly men at a male: female-and-young-people ratio of 4:1.^{1,3} and has become a public health problem because it involves long-term treatment, high costs in care, and leads to a negative affectation in the patient and his family. The majority of patients affected with SCI cannot recover lost functions because the CNS, unlike the Peripheral Nervous System (PNS) once affected presents irreversible changes that hinder nerve regeneration.^{2,5}

This article intends to describe a review of the pathophysiological considerations found in the scientific literature, which are developed in patients with SCI.

Physiopathology

To describe the pathophysiology of SCI, the types of lesions that the spinal cord can undergo must be known, classified as follows: solid cord injury, contusion, laceration, and massive compression; with contusion being the most common SCI representing between 25% and 40% of the cases. In the majority of these, the anatomic severity of the damage does not correlate with the degree of loss of functional abilities presented by the patient.^{6,7}

SCI are a two-step process involving primary and secondary mechanisms, the latter being first described by Allen in 1911.⁸ The primary process includes the initial mechanical trauma due to the observed displacement of the structures of the vertebral column caused by direct energy, which causes axonal disruption, vascular damage, and cellular apoptosis. In the secondary process, progressive vascular changes are observed; these are caused by the initial trauma leading to the presence of edema and ischemia, accompanied by the liberation of free radicals and ionic alterations, with excitotoxicity as consequence.^{8,9}

The evolution of SCI undergo a series of changes divided into phases: immediate, acute, subacute, intermediate, and chronic.⁹

Primary injury

There are four mechanisms of primary injury: 1) impact with transient compression, 2) laceration-transection, 3) distraction, and 4) impact plus persistent compression; the last being the most common presentation.¹⁰

The first mechanism presents in patients with degenerative disease of the cervical spine suffering from hyperextension trauma. The laceration-transection may be due to firearm shot, displaced fracture, or stabbing wound. Distraction is the forced stretching of the spinal cord secondary to flexion, extension, rotation, or dislocation; it is more frequent in people with degenerative disease

of the cervical spine. Finally, the mechanism of impact plus persistent compression is observed in fractures with burst of vertebral body and retropulsion of bone fragments that exert compression in the spinal cord.¹⁰

Initial mechanical trauma includes tension and compression forces, causing penetrating injuries, strains, or tears in neural tissues and vascular structures.⁵ The initial impact results in the development of a hemorrhage that alters the blood flow, producing local infarcts due to hypoxia and ischemia, which harms the gray matter due to its metabolic requirements and differences in irrigation.^{5,10} The neurons located in the affected area suffer structural alterations and the myelin sheath diminishes, this, additional to the edema and the macrophages present in the area, are the factors that lead to the deterioration of the nervous transmission.⁵

Secondary injury

Theories about the secondary mechanisms have evolved in the last 30 years. In the 70s, the free radical hypothesis was crucial to the injury process as Demopoulos et al. stated. Later, in the 80s, they centered on the importance of calcium and lipid peroxidation. Presently, however, we're exploring the involvement of apoptosis, inhibition of intracellular protein synthesis, and glutaminergic mechanisms in the injury process.⁸

In 1911, Allen et al. observed there was a harmful agent present in the hemorrhagic fluid that could be causing damage to the spinal cord. This aroused the interest of different authors, which postulated physiological and biochemical mechanisms to explain the post-traumatic damage of the spinal cord tissue, such as: vascular changes, free radical formation, ionic imbalance, apoptosis, and inflammatory responses, among others.^{8,11}

Secondary spinal cord injury begins immediately, or minutes after injury, and can be extended for several days and even weeks.^{6,12} The tissue damage increases progressively, affecting the different levels of the spinal cord. In addition, endothelial damage leads to increased permeability and the

presence of intracellular edema, an important factor for the extravasation of the cells of the immune system.⁶

Trauma triggers a series of pathophysiological processes that induce secondary spinal cord injury. To achieve an adequate understanding, this process has been divided into phases taking into account the events that occur in each one of them.¹³

Immediate phase

This phase occurs within the first two hours. It begins at the time of trauma with detectable changes such as general inflammation in the spinal cord followed by hemorrhage in the central gray matter. The cells present necrosis by the mechanical disruption of the membranes and, in turn, ischemia due to vascular disruption. Sudden microvascular disruption causes bleeding in the white matter, aggravating the lesion due to the fact that it can spread and affect the adjacent or distal segments.¹³

Acute phase

This phase happens within 2 to 48 hours. In the acute phase the primary damage occurs as a direct result of trauma, and once the structural thresholds are overcome, immediate cellular and biochemical alterations begin to happen.^{12,13} This phase is marked by systemic and local alterations such as alterations of the vascular mechanisms, ionic imbalance, and immune system response, among others, which will be described next.^{12,13}

Free radicals

The production of radicals from the lipid peroxidation of the cell membrane in the lesions of the central nervous system causes enzymatic deterioration dependent on phospholipids, alterations in the ionic gradients, and even lysis of the membranes.⁸ In addition, they play an important role in post-traumatic hypoperfusion since there is a reduction of the blood flow of the spinal cord leading to the appearance of edema and an inflammatory response.¹¹ Oxidative stress disables key mitochondrial enzymes in processes such as the respiratory chain,⁸ production of DNA-associated-proteins due to their nitration,⁶ and

inhibition of Na⁺/K⁺-ATPase inducing a metabolic collapse and, therefore, the necrotic or apoptotic death of the cell.¹⁴

The use of high doses of methylprednisolone within the first eight hours has been found to improve spinal cord blood flow and microvascular perfusion, contributing to clinical neurological recovery.⁸ In this way, their routine use in clinical practice is still questionable. On the other hand, the cytoprotection through inhibitors of lipid peroxidation facilitates the maintenance of neuronal excitability and inhibits the vasoconstrictor effect produced by prostaglandins.^{8,11}

Vascular mechanisms

The injury causes a reduction of the blood flow, and therefore progressive ischemia, during the first hours, possibly associated to the vasospasm induced by mechanical damage.^{8,10} White matter perfusion decreases the first five minutes, re-establishing at approximately 15 minutes; however, in the gray matter there are multiple hemorrhages and intravascular thrombosis absencing flow during the first hour, and maintaining this the first 24 hours.¹²

The systemic hypotension resulting from the loss of hemodynamic self-regulation of the microvasculature may cause additional decreases in the blood flow of the spinal cord with induced hypertension that does not necessarily reverse ischemia but produces marked hyperemia at adjacent sites.^{10,14}

After the ischemic period, the medulla can present a period of reperfusion, which can exacerbate the injury due to the generation of free radicals and other toxic products that contribute to oxidative stress.^{10,14}

Ionic imbalance

Unregulated ion flow is detrimental to cell function and survival since the permeability of the cell membrane is compromised by the activation of the protease.¹² In addition, high concentrations of intracellular Ca⁺ cause mitochondrial damage, enzymatic activation, changes in gene expression,

and apoptosis secondary to the activation of caspases, calpain, phospholipase A2, lipoxygenase, and cyclooxygenase.¹⁰⁻¹²

The failure of the Na⁺/K⁺-ATPase pumps, the activation of voltage-dependent Na⁺ channels, and the massive depolarization impede the mobilization of intracellular Na⁺ to extracellular space, producing, as a result, an activation of NMDA, AMPA, and Kainate glutamate receptors generating an excitotoxicity that damages oligodendrocytes and axons.^{6,14}

The increase of the extracellular potassium produces an excessive depolarization of the neurons, which affects the nervous conduction, being an important factor in the spinal shock. On the other hand, the decrease in magnesium affects metabolic processes such as glycolysis, oxidative phosphorylation, and protein synthesis.¹⁰

Lipid peroxidation

After the increase in levels of intracellular Ca⁺, the mitochondrial dysfunction, the degradation of arachidonic acid, and the activation of inducible nitric oxide synthase, the formation of reactive species of oxygen and nitrogen is produced, causing the peroxidation of lipids, damage of proteins and nucleic acids, inducing alterations in the cytoskeleton and organelles that lead to lysis and, therefore, to neuronal loss.¹²

Inflammatory response

After the trauma, the microglia cells induce leukocyte extravasation, which begins to release cytokines (such as tumor necrosis factor α , interleukin-6, and interleukin-1 β) complement and reactive species of the oxygen, allowing a greater extravasation and greater tissue damage.^{6,11,12,14}

These cytokines induce cyclooxygenase-2 expression by promoting the degradation of arachidonic acid in prostaglandins, prostacyclin, and thromboxanes that mediate permeability, vascular resistance, and platelet aggregation and adhesion. Excess cytoplasmic Ca⁺ activates the phospholipases so that they can produce arachidonic acid from the lipids of the cell membrane.^{6,14}

The inflammatory response is important for the elimination of cell debris, which may be vital in the regeneration of surviving neurons; however, an exaggerated response damages healthy tissue and exacerbates the lesion.¹²

Microglial cells, neutrophils, and macrophages offer innate immunity, and lymphocytes offer adaptive immunity. Neutrophils enter the damaged spinal cord immediately after the injury and peaks at six hours. Macrophages remain elevated within two to seven days and persist for up to two weeks after the injury.⁶

Apoptosis

Apoptosis is a form of programmed cell death characterized by cellular shrinkage, chromatin aggregation, and nuclear pyknosis, mediated by the activation of enzymes called caspases.¹⁴ During the acute phase the process of cellular inflammation and then rupture of the cell membrane lead to cell death by necrosis immediately; after several hours the caspase cascade is activated in neurons, oligodendrocytes, microglia, and astrocytes.^{10,12} In trauma, apoptosis occurs at the epicenter of the lesion and areas of Wallerian degeneration in the white matter, even after several weeks, contributing to post-injury demyelination.^{8,11,14}

Inhibition of protein synthesis with cycloheximide has been found to inhibit apoptosis, reduce secondary damage, and improve functional outcome after spinal cord injury, which demonstrates the requirement for the cell to actively contribute to its own apoptotic disappearance stemming from the synthesis of new proteins.¹⁴

Subacute phase

The phase lasts approximately from two days to two weeks, in which the phagocytic response increases in order to achieve a removal of the débrided tissue in the area of the lesion, allowing a possible axonal regeneration.¹⁵ In addition, the astrocytic response occurs late due to hyperplasia and hypertrophy of the astrocyte population around the lesion, which will form the glial scar, which represents the physical and chemical barrier to axonal regeneration and promotes the restoration of ionic maintenance.¹⁶

Intermediate phase

This phase lasts approximately from two weeks to six months, characterized by the maturation of the glial scar produced by the late astrocytic response. In addition, this reaction of the astrocytes allows the possible regeneration of the affected axons to continue, but is insufficient for recovery in severe lesions.¹⁷

Chronic phase

The degenerative process continues and extends to the areas surrounding the lesion, which present depressed electrical and functional activity evolving to what is known as secondary injury and thus a subsequent loss of neuronal function. The trauma -in addition to producing neuronal death- provokes lysis of glial cells, destruction of blood vessels, and lesions in axonal tracts that, when unable to regenerate, cause the alterations to be permanent.¹⁸

The process of demyelination begins 24 hours after injury, increasing two weeks later due to the effect of inflammatory cells entering a second phase of migration.¹⁹ At the third week, some fibers present Wallerian degeneration and loss of axonal diameter. The immature forms of healthy oligodendrocytes are able to re-myelinate some axons; additionally, the Schwann cells release trophic factors that collaborate with this process.^{18,20}

Neurogenic shock

It is defined as a systolic blood pressure <100 mmHg associated with a heart rate <80 bpm in the context of medullary trauma, with sudden loss of autonomic tone resulting from the injury due to damage in the sympathetic nervous system (cervical or high thoracic SCI).^{21,22} It manifests clinically with hypotension, bradycardia, circulatory collapse due to decreased peripheral vascular resistance, and compromise of cardiac output.^{6,10}

The mechanical trauma produces a direct compression of the CNS and peripheral elements by the osteoligamentous structures; additionally, there is damage to vessels, axons, and rupture of nerve cells' membranes. Secondary to the

triggered inflammatory process, ischemia of the spinal cord is presented; later, the regulation of the blood flow of the tissue ceases leading to systemic hypotension, exacerbating the ischemia and the progression of the spinal injury.²² Hypotension and neurogenic shock after acute spinal injury is a distributive process resulting from loss of peripheral vasoconstrictor tone in the arterioles and accumulation of blood within the peripheral vasculature.¹²

Spinal shock

It is a post-trauma neurophysiological condition generated by neuronal hyperpolarization, making them insensitive to the brain stimuli, showing as lost function and reflex activity below the level of the injury.^{6,19} The clinical picture is characterized by the presence of flaccid paralysis, areflexia, loss of sympathetic tone producing bradycardia, hypotension and absence of the cavernous bulb reflex.⁶ These symptoms will remain until the reflex arcs below the level of the injury resume their functionality.³ Spinal shock can be divided into four phases: areflexia/hyporeflexia; initial reflex return; early hyperreflexia; and late hyperreflexia.⁶

Conclusion

In the pathophysiology of SCI, a series of events such as free radical production, vascular alteration, ionic imbalance, lipid peroxidation, immune system response and apoptotic induction are present, chronologically distributed in the phases described above. Other hemodynamic alterations can present, such as neurogenic and spinal shock, affecting the prognosis of these patients.

Knowing the phases of the spinal cord injury gives the physician an idea of the physiological events that are possibly occurring, which allow him to make an adequate selection of the interventions that could possibly improve the neurological prognosis of the patient.

Conflict of interest

There are no conflicts of interest for any of the authors in this scientific report.

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