Chapter

Physiopathology of Spinal Cord Injury

Susana Martiñón, Juan Armando Reyes-Perez and Psyché Calderón-Vargas

Abstract

Spinal cord injuries have a multifactorial process with diverse evolution over time. An acute injury produces severe pathological and physiological changes in the organism, homeostasis is recovered, and both adverse and favorable reactions occur for the individual. In this chapter, we describe the pathophysiological follow-up to spinal cord injuries, from their acute to chronic presentations. The importance of this knowledge lies in finding solutions to the multiple disorders generated from a spinal cord injury. These will depend on the specific needs of each stage, considering the intensity of the injury, and the time elapsed from the beginning of the process until years later.

Keywords: spinal cord injury, anatomy, physiology, pathophysiology

1. Introduction

Spinal cord injury represents a devastating impairment in the patient's life that it is also known to include the patient's family. Adapting to the new condition is a challenge for all who are involved, as it is especially expensive from the economic point of view, not only for the patient and his family but also for health services, as it involves expenses of a diverse nature to offer the best quality of life for the patient. In addition, the majority of patients who suffer from it are of a productive age, which implies the need to abandon their sources of income, depending totally on their family, both financially and on their basic survival needs, such as eating, getting dressed, bathing, etc., even needing in-home specialized health care. According to various epidemiological studies, spinal cord injuries affect between 236 and 1298 patients per million inhabitants in different countries [1].

Spinal cord injury is caused by three experimental mechanisms, contusion, compression, and hemisection, all of these representing clinical lesions for study [2]. All three have different degrees of primary tissue damage; however, the three trigger severe secondary mechanisms that amplify tissue damage, hindering and even preventing the regeneration of damaged tissue. In this review, an approach is made to these destructive mechanisms after a spinal cord injury, with the aim of providing the bases of the pathophysiology of spinal cord injury to aid in decision-making for implementation of clinical and/or experimental treatments.

2. Methodology

A systematic search was conducted in PubMed and Embase with the following MeSH terms and keywords: "spinal cord injury and hemorrhagic," "spinal cord injury and secondary damage," "spinal cord injury and pathophysiology," "spinal cord injury and ischemic effects," "spinal cord injury and ionic dysregulation," "spinal cord injury and free radicals (FR)," "spinal cord injury and excitotoxicity," and "spinal cord injury and electrolyte imbalances." The search results were refined, selecting published articles from renowned journals in the medical and scientific areas that are less than 10 years old. Twenty-six studies were selected.

3. Pathophysiology of traumatic injury in the spinal cord

After a mechanical spinal cord injury (primary lesion), a series of self-destructive mechanisms (secondary lesion) is triggered that cause greater destruction of the spinal cord parenchyma with long-term sequela. Spinal cord injury is associated with mechanical damage, biochemical disorders, and hemodynamic changes [3]. The anatomic point where the primary lesion is exerted is known as the "epicenter," and the secondary mechanisms develop in a centrifugal form around the epicenter, expanding the injured area (**Figure 1**).

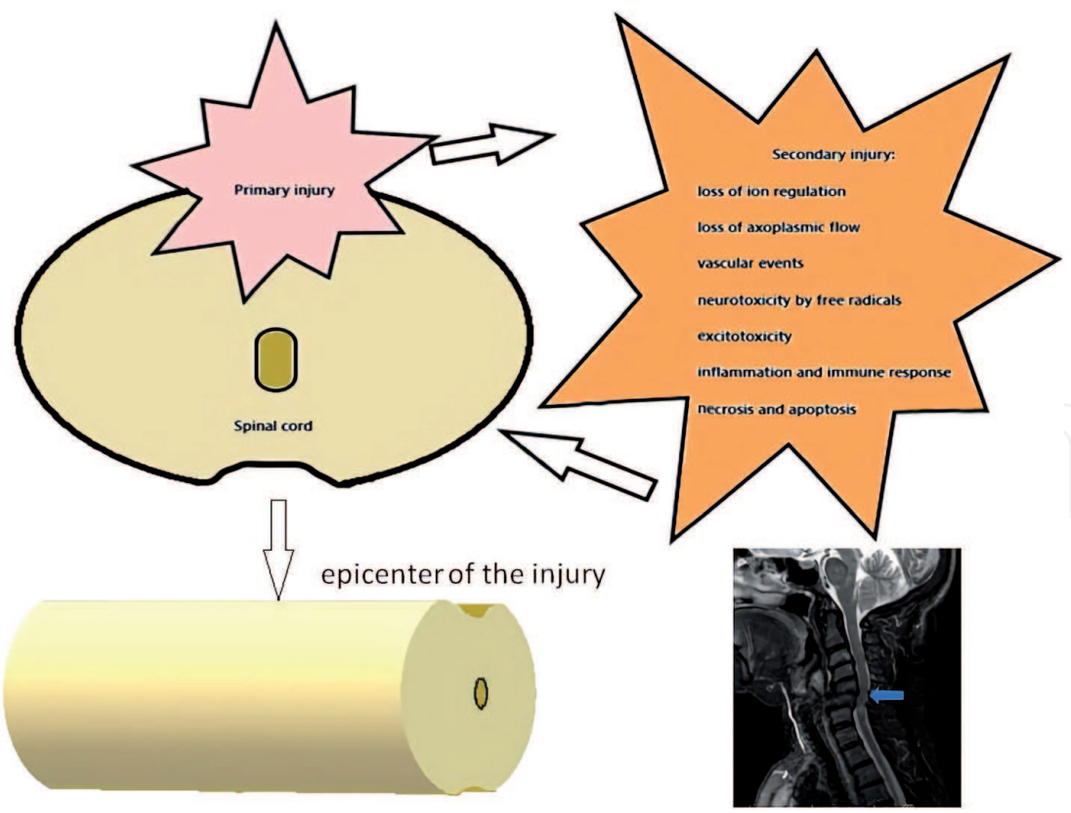

Figure 1.
Schematic summary of spinal cord injury. The primary lesion is the result of trauma directly on the neural tissue, anatomically called the epicenter of the injury to the point where the spinal cord is affected by the primary lesion; this injury triggers a series of destructive events known as a secondary injury, which will increase the area of injury in a centrifugal way, magnifying the systemic effects; these events can be observed years after the primary lesion.

3.1 Loss of ion regulation

Some of the histological changes that are observed after a TSC are the formation of edema and softening of the tissue, increase in the concentration of water, change in the caliber of the blood vessels, and rupture of the myelin surrounding the axons, in addition to a decrease in axoplasmic flow [4], with loss of ion regulation, in which an intense movement of ions is observed through an electrochemical gradient in which the concentrations of sodium (Na^+) and calcium (Ca^{2+}) increase and potassium (K^+) and magnesium (Mg^+) decrease at the intracellular level. When the gradient is altered, the electrical conduction ceases immediately, and the formation of edema is stimulated [5]. In addition, the increase in free intracellular Ca^{2+} triggers cell death by inhibiting mitochondrial function. It decreases the activation of ATP by activation of ATPase, protease, and phospholipases, with the resulting catabolism of proteins and structural lipids and inhibition of axoplasmic transport, because the increase of Ca^{2+} in the axoplasm triggers the action of neutral proteases activated by this ion and massive proteolysis of neurofilaments, which can lead to progressive collapse and fragmentation of the axon, causing tissue necrosis [6].

3.2 Necrosis and apoptosis

Activation of calpains and caspases represents other activation mechanism processes of necrosis and apoptosis by increasing intracellular Ca^{2+} [7]. The calpains constitute a superfamily of non-lysosomal proteases dependent on Ca^{2+} with a cysteine in its catalytic site. They are encoded by around 14 independent genes and have been attributed to various functions as the anchor of membrane proteins, signaling cascades, cytoskeleton remodeling, and apoptosis. The importance of caspases is the activation to start the process of programmed cell death; this has been demonstrated in deficient caspase-3 and caspase-9 mice [8].

3.3 Loss of axoplasmic flow

The axonal flow is modified because of axonal breakage. The axoplasmic flow can be retrograde or anterograde, both of which are fundamental for neuronal function. Although the cytoskeleton is composed of microtubules, actin filaments, and intermediate filaments, only microtubules are involved in the transport of materials through axons [9]. The anterograde transport is carried out through proteins associated with the cytoskeleton called kinesins, and it happens at a speed between 50 and 400 mm/day, while retrograde transport is through proteins known as dyneins [10]. The main molecules that are transported through the axons are synaptic precursor vesicles and dense core vesicles, signaling endosomes, BDNF vesicles, endosomes, late lysosomes, autophagosomes, APP, mRNA, neurofilament, and tubulin assembly and cytosolic proteins, in addition to organelles such as mitochondria [9]. Axonal fragmentation resulting from the traumatic spinal cord injury makes it impossible for the neuron to send these in both directions, which generates growth abortion and no axonal regeneration, conjointly with the formation of a fibroglial scar in the area of injury [11].

3.4 Vascular events

As mentioned earlier, the ischemic process is another mechanism through which secondary damage occurs. One of the achievements of modern vascular neurology

is the description of the vascular, cellular, and biochemical changes that constitute this process [12]. The primary spinal cord injury generates a spinal cord shock, with the consequent neurogenic shock. According to Popa [13], a systemic vascular response is generated when the following are observed: coronary heart disease, arterial hypotension, and deep vein thrombosis, which may be perpetuated to become chronic processes.

Ischemic damage is constituted by the dynamic interaction between neurons, astrocytes, fibroblasts, smooth muscle, and endothelial cells that interact with the formed elements of the blood leading to cell death [12]. The main biochemical events that occur in this ischemic process are inhibition of protein synthesis, depression of intracellular energy reserves, depolarization of the cell membrane, release of intracellular K^+ followed by the release of neurotransmitters, Ca^{2+} influx to the cell, and cellular metabolic commitment, which leads to lipidic peroxidation that ultimately results in neuronal nuclear destruction and death. At the molecular level, an increase in oxygen extraction increases glucose demand, and lactic acidosis is expressed [14].

3.5 Neurotoxicity by free radicals

Another mechanism that contributes in a very important way to the increase in damage in the area of injury is the neurotoxicity caused by free radicals. These reactive molecules are powerful oxidizing agents that are in balance with antioxidant systems. They have one or more unpaired electrons due to their loss or gain, which makes them very unstable, and they are responsible for damage to cell structures of biological importance [13, 15]. The free radical species that can be found include superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^-), ozone (Oz), nitric oxide (ON), hypochlorous acid (HOCl), and different metal ions. These ions are generated in the mitochondria during oxidative phosphorylation which is a process whereby ATP is formed as a result of the transfer of electrons from NADH or $FADH_2$ to oxygen through a series of electron transporters [16].

The free radical-mediated tissue injury is the result of abnormal and uncontrolled reactions of these molecules in several cellular compartments. The activity is divided into three stages: initiation, propagation, and termination [17].

The initiation of lipoperoxidation is by extraction of a hydrogen atom from the allylic carbons (= C—) of the unsaturated fatty acids of the cell membranes as well as the purine bases and pyrimidine bases of the nucleic acids, resulting in free radical alkyl (R.). Free radicals alkyl rearrange molecularly forming a conjugated diene that will react with molecular oxygen generating peroxyl radicals ($ROO^{\cdot}$) [18] which by extraction of one hydrogen atom from another allylic carbon, from another unsaturated fatty acid from the bilayer lipidic biological membranes reacting to hydroperoxides forms (ROOH) involving the process called propagation. Finally, the termination phase occurs by the formation of aldehydes, hydrocarbonaceous gases, and various chemical residues, including malondialdehyde (COH—CH_2—CHO) which will react with lipids and proteins to form conjugated Schiff bases, insoluble products that accumulate inside the lysosomes and form the pigment known as lipofuscin [19].

As will be seen below, the immune response after spinal cord injury recruits a large number of inflammatory cells, including neutrophils and macrophages, which are producers of nitric oxide. Nitric oxide is a free radical that is very important for vascular physiology since it participates in numerous regulatory events, which include vascular tone and blood pressure. This radical is formed by the reaction of L-arginine and oxygen and cofactors such as NADPH, and this reaction is catalyzed by nitric oxide synthase (NOS). Nitric oxide synthase has three isoforms: nNOS (present in brain neurons), eNOS (in endothelial cells), and iNOS (inducible in the

macrophage); the first two are dependent on high concentrations of Ca^{2+} and have a physiological function, while the latter is independent of Ca^{2+} and is important in inflammatory processes [20].

Among other consequences, the alteration in the basal levels of NO produces cell death, and, although the mechanisms are not totally clear, it is known that apoptosis can occur from the inhibition of glycolysis, the Krebs cycle, and the synthesis of the DNA; also, when combined with superoxide radical, peroxynitrite is formed ($O_2^- + NO \rightarrow ONOO^-$), which is a highly reactive species and cytotoxic, as it reacts with proteins, fatty acids of membranes, and nucleic acids and decomposes into products with toxic substances that may include nitronium ion (NO_2^+), nitrogen dioxide (NO_2), and hydroxyl ion (OH^-) [16].

In this regard there are protective systems that prevent the excessive increase of oxidizing species. Among them there are three enzymes that are the most important system of this protection: superoxide dismutase (SOD), which converts the superoxide radical into hydrogen peroxide; the glutathione peroxidase, which using two molecules of glutathione in the reaction converts hydrogen peroxide into two water molecules, while the lipid peroxides are reduced in the presence of glutathione; and finally catalase, which also destroys hydrogen peroxide. However, the activity of these antioxidant enzymes is particularly low in the CNS compared to other tissues [21]. This makes this system particularly sensitive to free radicals. In addition, the CNS is rich in iron, which is the main inducer of the production of free radicals after an injury to the CNS itself. On the other hand, the cellular membrane of tissues is rich in cholesterol and polyunsaturated fatty acids which are targets of oxygen free radicals. Likewise, the CNS has few antioxidant defenses, which causes it to be even more vulnerable; in addition, studies in patients have shown that during the first year after injury, oxidative stress increases and the ability of the antioxidant defense decreases [22].

3.6 Excitotoxicity

Another mechanism of cell damage after spinal cord injury is known as excitotoxicity, caused by excessive release of neurotransmitters. A continuous increase in glutamate concentrations is observed, due to the self-amplification of glutamatergic circuits. These circuits function due to the recycling of glutamate, exocytosis of calcium-dependent synaptic vesicles, and discharge of intracellular glutamate as a result of cell lysis [23]. This abundance of glutamate, especially in a hypoxic environment, overstimulates its ionotropic receptors, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA), and kainate, triggering cell death by excitotoxicity [24].

Initially, glutamate binds to its receptors and causes depolarization. This activates voltage-dependent sodium channels, causing extensive depolarization and a marked increase in intracellular sodium concentration. The chronicity of this response will lead to the release of NMDA receptors from their blockade by magnesium, leaving them available for activation by glutamate and increasing intracellular sodium. This intracellular imbalance of ions, caused by the flow of sodium, is corrected by a flow of chloride ions. In addition, this attempt to restore the osmotic balance of the cell leads to a flow of water into the intracellular space causing lysis [24]. Alternatively, excitotoxicity can kill neuronal cells by calcium-dependent mechanisms. This means that chronic depolarization leads to an intracellular calcium flux via calcium-dependent channels and the opening of channels of NMDA receptors; this flow is increased by the mobilization of calcium from its intracellular reservoirs and the reverse sodium-calcium exchange operation of the membrane, and activation of calcium-dependent self-destructive enzymes begins as a result [22].

Cell death by excitotoxicity is also observed in the glia [24], oligodendrocytes being the most susceptible cells [25]; as these cells do not have NMDA receptors, excitotoxicity is via AMPA, and kainite receptors in oligodendrocytes are more permeable to calcium in neurons, resulting in a more accelerated destabilization of their organelles; in addition, these cells have less efficient calcium buffering systems, which generate cell death in a more hasty manner [25].

3.7 Inflammation and immune response

After a TSC an intense inflammatory response is triggered that involves the action of chemical mediators, the cytokines IL-2, IL-6, and tumor necrosis factor alpha (TNF-α), and the participation of inflammatory cells such as neutrophils and mast cells. In addition to a large invasion of macrophages to the site of injury, both activated neutrophils and macrophages produce superoxide anion and nitric oxide; the latter can also be produced by platelets, endothelial cells, and microglia (CNS macrophages). Activated macrophages/microglia are important producers of cytotoxic substances, such as the proinflammatory cytokines mentioned above, causing neural damage and preventing tissue regeneration [26]. According to David [2], a flow of monocytes to the spinal cord of mice occurs at 12 hours and again at 4 days after injury. This flow is dependent on MYD88 and IL-4; however, it is not well determined whether it is from proinflammatory monocytes. In rats, researchers have been able to track dendritic cells to the area of injury by immunofluorescence, though it has not been seen in mice.

4. Discussion

The pathophysiology of spinal cord injury is not sufficiently described, and further research is needed to gain a better understanding of all the processes involved.

However, the mechanisms known so far show us a multifactorial syndrome that requires detailed study of destruction phenomena that are triggered as secondary injury. The understanding of these phenomena will lead to the rational search for solutions for patients with this condition. It is important to emphasize finding therapies that help the patient in both moments of the evolution of the lesion, as well as to provide neuroprotection, so as to favor the regeneration of injured tissue. In this chapter a brief description of the pathophysiology of the spinal cord lesion is offered in order to help the researcher find the best solutions.

There are a large number of studies with different approaches. However, a solution to all the consequences that a spinal cord injury causes has yet to be found, and so the need to find alternative treatments remains.

5. Conclusions

All the alterations and phenomena that occur at a cellular and molecular level are related to gradual degeneration of both vascular and neural tissue, destroying the anatomical substrate necessary for neurological recovery. These neurodegenerative processes cause the need to use different therapeutic strategies that reduce the damage caused by secondary injury, always looking for alternatives based on an understanding of the pathophysiology of spinal cord injury, which helps generate comprehensive and multivariable treatments that favor the recovery of function, preventing secondary damage and favoring regeneration of the neural tissue.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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