Florez-Perdomo *et al.*
Egyptian Journal of Neurosurgery (2024) 39:27
https://doi.org/10.1186/s41984-024-00282-9

Egyptian Journal of Neurosurgery

REVIEW Open Access

Pathobiology of traumatic spinal cord injury: an overview

William A. Florez-Perdomo[1,4*], Andrés Cardona-Cruz Guillermo[1], Ezequiel García-Ballestas[1,4], Abigail Castilla-Martínez[1], Yancarlos Ramos-Villegas[1,2], Loraine Quintana-Pájaro[1,2], Tariq Janjua[5], Amit Agrawal[3] and Luis Rafael Moscote-Salazar[1]

Abstract

Traumatic spinal cord injury (SCI) or traumatic myelopathy is a devastating neurological condition and a heavy burden on the health system. There are inflammatory and structural biomarkers with well-defined profiles, and useful for determining the management and prognosis of this pathology. Laboratory studies have shown some utility in confirming the existence of a spinal cord injury. Little knowledge about the molecular processes that occur after a SCI is evident, and it is well known that its understanding is dispensable to establish therapeutic targets that improve the outcomes for this type of patient. Many studies have explored the role of structural and inflammatory markers and some structural and inflammatory biomarkers. In the present article, we review the ongoing research in the field of spinal injury and possible role of biomarkers in the management of these patients.

Keywords Spinal cord injury, Spinal trauma, Traumatic myelopathy, Biomarkers

Introduction

Traumatic spinal cord injury (SCI) or traumatic myelopathy is a devastating neurological condition, imposing a significant burden on the healthcare system [1, 2]. SCI leads to varying degrees of motor and sensory deficits, and in some cases, autonomic dysfunction [3, 4]. The spectrum of spinal cord injuries ranges from subclinical injuries to complete transection [5–7], resulting in varying degrees of motor, sensory, and autonomic dysfunctions, including bowel, bladder, and sexual dysfunctions [6–10].

Classically, the initial evaluation of a patient suspected of having SCI follows the recommendations outlined in the protocol for life support of traumatic spinal injuries, commonly known as the ABCDEs of traumatic injuries [2, 11]. Throughout history, various classifications have been proposed [10], and in some instances, clinical judgment alone guides the management of cervical injuries when radiological findings are inconclusive [12].

Given the profound impact of SCI on patients' lives and the healthcare system, there is a pressing need for innovative approaches to diagnosis and treatment. Numerous studies have investigated the role of structural and inflammatory markers, as well as various biomarkers [13]. In this article, we provide an overview of the current research in the field of spinal injury and explore the potential role of biomarkers in the management of these patients. This review aims to shed light on the importance of ongoing research and its potential to enhance the care and outcomes of individuals with SCI.

*Correspondence:
William A. Florez-Perdomo
Williamflorezmd@gmail.com
[1] Colombian Clinical Research Group in Neurocritical Care, Bogota, Colombia
[2] Regions Hospital, Saint Paul, USA
[3] Department of Neurosurgery, All India Institute of Medical Sciences, Saket Nagar, Bhopal 462020, Madhya Pradesh, India
[4] European Stroke Organisation ESO, Basel, Switzerland
[5] Department of Critical Care Medicine, Physician Regional Medical Center, Naples, FL, USA

Inflammatory changes in SCI

Traditionally, it was believed that the damage caused by a spinal cord injury (SCI) was confined to the direct mechanism responsible for the lesion, and this was thought to account for all clinical aspects of the patient, including their prognosis [14]. However, recent studies have revealed that there exists a phase following the initial injury, the duration of which can vary, during which metabolic, vascular, and regenerative changes take place. These changes even impact the surrounding healthy tissue and are directly correlated with each patient's prognosis [14, 15].

The primary injury is characterized by the transfer of kinetic energy from a moving object, whether it is a projectile striking the individual or the individual colliding with an object, resulting in trauma to the spinal cord or lacerations caused by weapons [16]. Depending on the severity of the initial impact, a reactive process is triggered, allowing various cell types (T lymphocytes, macrophages, neutrophils) to migrate from the bloodstream to the site of the injury. These cells release proinflammatory cytokines (IL-6, IL-1, TNFα) that lead to apoptosis, necrosis, excitotoxicity, and the generation of free radicals. These cellular changes are secondary to mitochondrial dysfunction resulting from an increase in intracellular calcium levels in both neurons and glia [17].

Supporting these findings, a study conducted by Hasturk et al. in 2018 on rats demonstrated that Etanercept, a TNFα inhibitor, attenuated neuronal damage while also regulating IL-1 levels and increasing the intralesional concentration of antioxidant enzymes like superoxide dismutase [18, 19]. Additionally, it has been established that medullary tissue cells, such as astrocytes and microglia, can autonomously respond to harmful stimuli without the assistance of blood-borne cells [20].

Pathological response

Hemorrhage is the first disorder that alters the integrity of nervous tissue, which causes perivascular infiltration, increased adrenergic tone, activates platelets, and causes a prothrombotic state, while edema predominates in the white matter without associated changes. This leads to an inadequate blood supply, thus giving a hypoxic and ischemic tissue which is highly susceptible to reperfusion damage [16]. The cells involved in the inflammatory process are microglia and astrocytes [16]. Microglia is a cell type with phagocytic capacity that is sensitive to tissue damage and responds to it under two opposite phenotypes M1 (proinflammatory) and M2 (anti-inflammatory) depending on which substance stimulates them [21]. Resting microglia can differentiate to the M1 type by various proteins, such as LCN2 (lipocain-2) (acute phase protein) in the first hours after trauma, causing tissue damage, neuronal apoptosis, as well as glial and axonal damage through the release of cytokines such as IL-1, IL-6, IL-12, TNFa, TNFβ, glutamate, and reactive oxygen species [22]. On the other hand, IL-10 directs toward the M2 genotype, counteracting many functions of its counterpart, thus generating a balance between repair and destruction that can often be lost and lead to negative outcomes in patients suffering from SCI [23].

Role of biomarkers

Given the aforementioned limitations, research has contributed to the development of more affordable and more useful laboratory tools to initially evaluate the patient, estimate the degree of severity, and even objectively measure the response to treatment [13, 24]. To date, two types of biomarkers have been studied in the context of SCI: structural and inflammatory. The structural ones are compounds that are part of the nervous network and are released at the lesion site, diffusing into the cerebrospinal fluid (CSF) and occasionally into the blood; the inflammatory ones are cytokines, or fragments of them, that are released in the inflammatory response secondary to the trauma of the nervous tissue and can be found in the same samples [13].

Structural biomarkers

Neurofilaments

They are part of the axonal cytoskeleton and are classified depending on their molecular weight into light (68 kDa), medium (149 kDa), and heavy (200 kDa). [24]. Its polypeptide sequence is rich in serine, which is phosphorylated in pathological processes of nervous tissue [13]. After an axonal injury, various intracellular signaling pathways (calcium entry into the cytosol, caspase activation) alter the stability of the axonal skeleton, releasing cytosolic components to the outside and then into the CSF and blood [24]. Elevation of this marker in the serum of rats with SCI has been shown in comparison to healthy rats, reaching maximum concentrations on the second day [24]. Interestingly, the presence of low concentrations of phosphorylated neurofilaments in early stages has been associated with a better prognosis, such that in humans, the levels of phosphorylated neurofilaments in CSF are directly proportional to the severity of the lesion and are associated with a worse prognosis [13].

Tau protein

It is a protein that is part of the microtubules in the axon of the neuron and participates in anterograde axoplasmic transport and is elevated in the CSF of patients with SCI compared to healthy patients, both in its intact and cleaved form (this last by the proteolytic action of calpain

1 and caspase 3) [13, 24]. Other studies analyzed the levels of this protein in patients with SCI (complete and incomplete) and showed that after 24 h, the levels of Tau protein were associated with a more severe lesion, as well as with motor recovery of the patient at 6 months [25]. Since the serum levels of this protein and its cleaved form are 10 times lower than those present in CSF depending on renal clearance, the CSF/serum concentration ratio is useful to assess the integrity of the blood–brain barrier [13, 24].

Enolase neurospecific

It is a neuronal glycolytic enzyme that predominates in the neuronal soma that under normal conditions does not leave the cell; therefore, its detection in the CSF or serum is indicative of neuronal damage [13]. It has been found elevated in rats with SCI, reaching a maximum concentration peak between 6 and 24 h [13, 24] It has been little investigated and has shown a poor prognostic value.

Major basic protein (MBP)

It is part of the myelin sheath, is produced by oligodendrocytes, and constitutes 30% of the proteins that make up myelin [24]. This protein is degraded by various types of proteases released in the inflammatory process, and the resulting polypeptide chains are detected in CSF. In a study where rats underwent closed traumatic myelopathy, high serum MBP levels were reported at 3 h. The utility of this marker [13] remains uncertain S-100β protein. It is a calcium transporter protein produced by astrocytes and Schwann cells, but it is also present in numerous cell types outside the central nervous system and fulfills functions in the cell cycle, such as stabilizing the Tau protein [13, 24]. In animal models, the levels of S-100β in CSF and serum were elevated in the first hours, reaching maximum concentrations at 72 h; their concentration was also directly related to the severity of the injury. In humans, it has been studied in the context of decompressive surgeries, since it has been shown that the persistence of high titers of this substance is associated with unfavorable outcomes [13].

Glial fibrillary acidic protein

It is a monomeric protein belonging to the skeleton of the astroglia. It is specific for glial cells and is postulated as a marker of glial damage. Good results have not been shown in studies; however, it is considered a potential marker of neurological complications in the postoperative period of aortic aneurysm surgeries [13].

S-100β protein

The S-100β protein is a well-studied biomarker that has been investigated in the context of spinal cord injury (SCI). S-100β is a calcium-binding protein that is primarily found in astrocytes, a type of glial cell in the central nervous system (CNS) [13, 14]. When the CNS experiences injury or damage, such as in the case of SCI, S-100β is released into the bloodstream, making it a potential biomarker for assessing the extent of CNS injury.

Inflammatory biomarkers

MCP-1 (CCL2)

It is an important chemokine in the recruitment of type 1 monocytes [13]. In animal models with SCI, the codifying messenger RNA for MCP-1 is increased in the first 5 min in the spinal cord and becomes undetectable on the fifth day and is associated with the severity of the injury [13, 25]. In humans, elevated CSF levels have been found in the first 24 to 36 h in patients with both complete and incomplete SCI [13].

CXCL12

It is a cytokine that participates in neurodevelopment, neurite growth, and the signaling of inflammatory processes. [13, 25]. It is expressed in high concentrations in the dorsal corticospinal tract, posterior to the lesion site [25].

Tumor necrosis factor (TNF) and interleukin 1β (IL-1β)

They are proinflammatory cytokines responsible for various processes (proliferation, differentiation, and apoptosis) in addition to having pleiotropic effects [25]. In human experiments, high levels of both were found in the first 5 h after injury. They have high sensitivity, but low specificity [13, 25].

Oxidative Stress biomarkers

Malondialdehyde (MDA) is a product of lipid peroxidation, which is a process that damages cell membranes. Superoxide dismutase (SOD) is an enzyme that protects cells from damage caused by superoxide, a type of free radical [25–27].

Spinal cord injury (SCI) can lead to increased production of MDA and decreased activity of SOD. This can contribute to cell death and damage in the spinal cord [27].

MDA and SOD are being investigated as potential biomarkers for SCI. Biomarkers are substances that can be

measured in the blood or other bodily fluids to indicate the presence or severity of a disease [27].

Biomarkers of blood-spinal cord barrier dysfunction

Biomarkers of blood-spinal cord barrier (BSCB) dysfunction are important indicators used to assess the integrity and permeability of the barrier following spinal cord injury (SCI). The BSCB is similar to the blood–brain barrier and serves to protect the spinal cord from harmful substances and immune cell infiltration. When the BSCB is compromised due to injury or inflammation, various biomarkers can be measured to monitor its dysfunction. Some of these biomarkers include:

Vascular Endothelial Growth Factor (VEGF): VEGF is a signaling protein that plays a crucial role in angiogenesis and vascular permeability. Elevated levels of VEGF in the spinal cord following SCI are associated with BSCB disruption [27–33].

Claudin-5: Claudin-5 is a tight junction protein that helps maintain the integrity of the BSCB. Reduced levels or altered distribution of claudin-5 can indicate dysfunction of the barrier [29].

Albumin: Increased levels of albumin in the cerebrospinal fluid or blood can indicate leakage across the BSCB, as albumin is typically restricted to the bloodstream and should not enter the spinal cord parenchyma [30].

IgG (Immunoglobulin G): Detection of IgG in the spinal cord or cerebrospinal fluid is a sign of BSCB dysfunction, as antibodies like IgG are usually confined to the bloodstream [31].

Aquaporin-4 (AQP4): AQP4 is a water channel protein primarily found in astrocyte end-feet, and alterations in its expression or localization can be associated with BSCB disruption [32].

Tight Junction Proteins: Various tight junction proteins, such as occludin and ZO-1, can be measured to assess their expression and localization changes in response to BSCB dysfunction [33].

These biomarkers serve as valuable tools in diagnosing and monitoring the progression of SCI and can help guide treatment strategies aimed at preserving or restoring BSCB integrity. Monitoring these biomarkers can provide insights into the extent of damage and the potential for secondary injury following SCI.

Scope of research

Astrocytes are a diverse group of cells that have an important role in the late inflammatory process derived from SCI [26]. In this context, these cells have the capacity to adopt molecular, morphological, and functional changes depending on the severity of the condition. Thus, severe damage leads to increased expression of the glial fibrillary acidic protein and proinflammatory cytokines mentioned above, increases cell size (hypertrophy) constituting what is called "astrogliosis" [20]. The above is intended to form a physical barrier around the initial lesion site to delimit the extent of damage, but at the same time prevent axonal regeneration, producing Wallerian degeneration [20, 26]. Similarly, fibroblasts participate in the formation of the "fibrotic scar," where they secrete type I, III, and IV collagen, as well as fibronectin and laminin, giving greater structural support to the barrier [17]. In contrast to what is mentioned in this section, some studies suggest that the inflammatory process reactive to SCI may have neuroprotective effects for both the neuronal and glial populations, as is the case of M2 microglia [14, 23].

The role played by lymphocytes is poorly established, but it is generally accepted that the population of T lymphocytes over B is much higher [16]. The former can be differentiated into several lines depending on the type of cytokines they produce, with the Th17 line (IL-17-producing T lymphatics) being one of the most associated with secondary damage due to its neutrophil chemotactic function [14]. Following this, Jianzhong Hu et al., in a study carried out in rats in 2016, showed that the cytokine CCL20 (whose receptor is expressed in Th17 lymphocytes) aggravates tissue damage at the same time that it is a potential therapeutic target [14].

Conclusions

Little knowledge about the molecular processes that occur after a SCI is evident, and it is well known that its understanding is dispensable to establish therapeutic targets that improve the outcomes for this type of patient. SCI is a prevalent situation in our environment, and it is necessary for the healthcare team to properly manage these patients. The neurological physical examination helps to locate the lesion topographically, which must be consistent with the imaging findings and thus determine adequate management that includes the correct rehabilitation process. Knowledge of the inflammatory process after trauma is important for the development of both biological markers with good diagnostic performance (high sensitivity and specificity) and follow-up as well as active principles that regulate said response and improve the patient's prognosis. This possibly can help to translates into a better quality of life for both the patient and their family as well as lower health costs.

Abbreviations

SCI	Traumatic spinal cord injury
IL	Interleukin
TNF	Tumor necrosis factor
LNC2	Lipocain2
kDa	KiloDaltons
CSF	Cerebrospinal fluid
MBP	Major basic protein

RNA	Ribonucleic acid
MCP-1	Monocyte chemoattractant protein 1
CCL	Chemokine (C–C motif) ligand
Th	T lymphocytes helper
MDA	Malondialdehyde
SOD	Superoxide dismutase
IgG	Immunoglobulin G
AQP4	Aquaporin-4
VEGF	Vascular endothelial growth factor
BSCB	Blood-spinal cord barrier

Acknowledgements
None.

Author contributions
All the authors meet the authorship requirements, and they all made substantial contributions to conception of the manuscript regarding the contribution to conception and design, acquisition of data and the correspondent interpretation, drafting the article, and making the critically revision of the intellectual content.

Funding
Not applicable. There was no funding.

Availability of data and material
Not applicable.

Declarations

Ethics approval and consent to participate
The present manuscript has not been submitted to other journal for simultaneous consideration. The manuscript has not been published previously and is not split up in other parts, no data have been manipulated or fabricated, and no information is presented as if were from the authors.

Consent for publication
Valid informed written consent of the guardian was taken to publish this review. They were informed that the details of patient will not be disclosed.

Competing interests
No competing interest. The authors declare that they have no conflicts of interest.

Received: 27 February 2023 Accepted: 17 November 2023
Published online: 02 May 2024

References

1. Robert AA, Zamzami MM. Traumatic spinal cord injury in Saudi Arabia: a review of the literature. Pan Afr Med J. 2013;16:104.
2. Stein DM, Knight WA. Emergency neurological life support: traumatic spine injury. Neurocrit Care. 2017;27(Suppl 1):170–80.
3. De Smet E, Vanhoenacker FM, Parizel PM. Traumatic myelopathy: current concepts in imaging. Seminars Musculoskel Radiol. 2014;18(3):318–31.
4. Kirshblum SC, et al. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med. 2011;34(6):535–46.
5. Abouhashem S, et al. Management of Brown-Sequard syndrome in cervical disc diseases. Turk Neurosurg. 2013;23(4):470–5.
6. Brouwers E, et al. Definitions of traumatic conus medullaris and cauda equina syndrome: a systematic literature review. Spinal Cord. 2017;55(10):886–90.
7. Klakeel M, et al. Anterior spinal cord syndrome of unknown etiology. Proceedings. 2015;28(1):85–7.
8. Krassioukov A, West C. The role of autonomic function on sport performance in athletes with spinal cord injury. PM R. 2014;6(8 Suppl):S58-65.
9. Phillips AA, Krassioukov AV. Contemporary cardiovascular concerns after spinal cord injury: mechanisms, Maladaptations, and management. J Neurotrauma. 2015;32(24):1927–42.
10. Zhang S, et al. Spine and spinal cord trauma: diagnosis and management. Neurol Clin. 2013;31(1):183–206.
11. Rouanet C, et al. Traumatic spinal cord injury: current concepts and treatment update. Arq Neuropsiquiatr. 2017;75(6):387–93.
12. Szwedowski D, Walecki J. Spinal cord injury without radiographic abnormality (SCIWORA) - clinical and radiological aspects. Pol J Radiol. 2014;79:461–4.
13 Rodrigues LF, Moura-Neto V, Spohr TCLDSE. Biomarkers in spinal cord injury: from prognosis to treatment. Mol Neurobiol. 2018;55(8):6436–48.
14. Bang W-S, et al. Curcumin increase the expression of neural stem/progenitor cells and improves functional recovery after spinal cord injury. J Korean Neurosurg Soc. 2018;61(1):10–8.
15. Hu J, et al. C-C motif chemokine ligand 20 regulates neuroinflammation following spinal cord injury via Th17 cell recruitment. J Neuroinflammation. 2016;13(1):162.
16. Anwar MA, Al Shehabi TS, Eid AH. Inflammogenesis of secondary spinal cord injury. Front Cellular Neurosci. 2016;10:98.
17. Burnside ER, Bradbury EJ. Manipulating the extracellular matrix and its role in brain and spinal cord plasticity and repair. Neuropathol Appl Neurobiol. 2014;40(1):26–59.
18. Hasturk AE, et al. Etanercept prevents histopathological damage after spinal cord injury in rats. Asian J Neurosurg. 2018;13(1):37–45.
19. Aisen ML. Neurological rehabilitation. In: Handbook of clinical neurology. NJ: Elsevier; 2013. p. 229–37.
20. Fakhouri F. Neurosurgery under siege - Stories from Aleppo and the Syrian war: a narrative article. Asian J Neurosurg. 2017;12(2):342–3.
21. Ferreira AC, et al. From the periphery to the brain: Lipocalin-2, a friend or foe? Prog Neurobiol. 2015;131:120–36.
22. Thompson CD, et al. The therapeutic role of interleukin-10 after spinal cord injury. J Neurotrauma. 2013;30(15):1311–24.
23. Tabata H. Diverse subtypes of astrocytes and their development during corticogenesis. Front Neurosci. 2015;9:114.
24. Yokobori S, et al. Acute diagnostic biomarkers for spinal cord injury: review of the literature and preliminary research report. World Neurosurgery. 2015;83(5):867–78.
25. Kwon BK, et al. Cerebrospinal fluid inflammatory cytokines and biomarkers of injury severity in acute human spinal cord injury. J Neurotrauma. 2010;27(4):669–82.
26. Gaudet AD, Fonken LK. Glial cells shape pathology and repair after spinal cord injury. Neurotherapeutics. 2018;15(3):554–77.
27. Ozbilgin N, Goksel O, Atakisi O. The changes in cerebrospinal fluid levels of malondialdehyde and superoxide dismutase in patients with spinal cord injury. Neurochem Res. 2016;41(1):176–81.
28. Wang H, Wang Y, Li D, Liu Z, Zhao Z, Han D, Yuan Y, Bi J, Mei X. VEGF inhibits the inflammation in spinal cord injury through activation of autophagy. Biochem Biophys Res Commun. 2015;464(2):453–8. https://doi.org/10.1016/j.bbrc.2015.06.146. (**Epub 2015 Jun 24 PMID: 26116774**).
29. Montague-Cardoso K, Malcangio M. Changes in blood-spinal cord barrier permeability and neuroimmune interactions in the underlying mechanisms of chronic pain. Pain Rep. 2021;6(1):e879. https://doi.org/10.1097/PR9.0000000000000879.PMID:33981925;PMCID:PMC8108584.
30. Zhang Z, Li X, Wang X. Serum albumin as a biomarker for blood-spinal cord barrier dysfunction after spinal cord injury. J Clin Neurosci. 2018;51:249–53.
31. Xu X, Zhang X, Zhang Z. Serum IgG as a novel biomarker for predicting secondary injury after spinal cord injury. Spinal Cord. 2019;57(10):784–92.
32. Garcia TA, Jonak CR, Binder DK. The role of aquaporins in spinal cord injury. Cells. 2023;12(13):1701. https://doi.org/10.3390/cells12131701.PMID:37443735;PMCID:PMC10340765.
33. Jin LY, Li J, Wang KF, Xia WW, Zhu ZQ, Wang CR, Li XF, Liu HY. Blood-spinal cord barrier in spinal cord injury: a review. J Neurotrauma. 2021;38(9):1203–24. https://doi.org/10.1089/neu.2020.7413. (**Epub 2021 Feb 16 PMID: 33292072**).

Publisher's Note