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# Essentials of Spinal Cord Injury Medicine

*Edited by Yannis Dionyssiotis*

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http://dx.doi.org/10.5772/68029
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First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Essentials of Spinal Cord Injury Medicine
Edited by Yannis Dionyssiotis

p. cm.

Print ISBN 978-1-78923-248-6

Online ISBN 978-1-78923-249-3

eBook (PDF) ISBN 978-1-83881-275-1

# Meet the editor

Dr. Yannis Dionyssiotis is specialized in Physical Medicine and Rehabilitation. He holds his PhD degree in SCI-induced Osteoporosis-Metabolic Bone Diseases from the Laboratory for Research of the Musculoskeletal System (University of Athens). He worked as a consultant physiatrist and a medical director in KAT Hospital in Athens, Rhodes General Hospital and Rehabilitation Center of Florina, Greece, and in the Klinik für neurochirourgische-neurologische Frührehabilitation, Westpfalz-Klinikum, Germany, respectively. Currently, he is the head of Rehabilitation Department of European Interbalkan Medical Center, Thessaloniki, Greece. He is elected in the board of International Society of Musculoskeletal and Neuronal Interactions (ISMNI), of Prevention Committee of International Spinal Cord Society (ISCOS), and has written books and papers on spinal cord injury, multiple sclerosis and so on (http://publicationslist.org/y.dionyssiotis).

# Contents

# Preface

It is my privilege to be the editor of the book *Essentials of Spinal Cord Injury Medicine.* This book is a sequel to our previous IntechOpen publication *Topics in Paraplegia* and includes seven new chapters about spinal cord injury starting from basic knowledge, functional anatomy to medical complications, which limit rehabilitation potential and new research in spinal cord injury.

Spinal cord injury is a severe, often life-threatening traumatic condition leading to serious neurological dysfunctions. The first chapter presents the pathological hallmarks of spinal cord injury, which includes inflammation, reactive gliosis, axonal demyelination, neuronal death, and cyst formation. Understanding the pathophysiology of injury will improve our knowledge in neuroprotection and neuroregeneration leading to better rehabilitation prognosis. Important data on therapeutic strategies in preclinical and clinical phases, targeting mechanisms in acute and chronic stages of SCI, as well as their limitations and advances are presented in the second chapter. The third chapter describes the medical etiologies and treatments for spastic paraplegias due to nontraumatic spinal cord disorders. Because of aging, epidemiological studies have found, mainly in developed countries, a shift in the causes of spinal cord injury from traumatic to nontraumatic, which may overtake traumatic in the next decade. The next chapter discusses penetrating spinal cord injury, which is a relatively rare entity affecting mainly young males, and in the fifth chapter, infectious complications after spinal cord injury and the preventive role of rehabilitation are analyzed.

Finally, the last two chapters include new data about powered exoskeletons, which provide patients with SCI the ability to walk with lowest energy consumption, and last but not least, a chapter with preclinical and clinical updates of cellular transplantation that majorly involves cells' population derived from human embryonic stem cells, mesenchymal stem cells, and human-induced pluripotent stem cells, the extent of success from cellular transplantation, associated controversies, and other emerging technologies concludes the project. As clinicians, we are often facing the problem subjected to spinal cord injury to rely on us to provide information about new therapies or novel possibilities. I would like to thank all the authors who participated and IntechOpen, especially Ms. Kristina Kardum, for the kind cooperation in the development of the project.

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Chapter 1

# Understanding Molecular Pathology along Injured Spinal Cord Axis: Moving Frontiers toward Effective Neuroprotection and Regeneration

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http://dx.doi.org/10.5772/intechopen.72118

**Abstract**

Spinal cord injury (SCI) is a severe, often life threatening, traumatic condition leading to serious neurological dysfunctions. The pathological hallmarks of SCI include inflammation, reactive gliosis, axonal demyelination, neuronal death, and cyst formation. Although much has been learned about the progression of SCI pathology affecting a large number of biochemical cascades and reactions, the roles of proteins involved in these processes are not well understood. Advances in proteomic technologies have made it possible to examine the spinal cord proteome from healthy and experimental animals and disclose a detailed overview on the spatial and temporal regionalization of these secondary processes. Data clearly demonstrated that neurotrophic molecules dominated in the segment above the central lesion, while the proteins associated with necrotic/apoptotic pathways abound the segment below the lesion. This knowledge is extremely important in finding optimal targets and pathways on which complementary neuroprotective and neuroregenerative approaches should be focused on. In terms of neuroprotection, several active substances and cell-based therapy together with biomaterials releasing bioactive substances showed partial improvement of spinal cord injury. However, one of the major challenges is to select specific therapies that can be combined safely and in the appropriate order to provide the maximum value of each individual treatment.

**Keywords:** spinal cord injury, secondary processes, proteome, biomaterials

## 1. Introduction

Intensive lifestyle brought about by the modern age of the twenty-first century often brings risks of trauma to the CNS. Both trauma of brain and spinal cord are considered not only as life-threatening conditions, but also as substantial, social, and economic problems that affect mainly the young population. The increased incidence of trauma may be related to popular sports such as ice hockey, American football, rugby, horse riding, and diving, but the most common causes include traffic accidents [1]. Spinal cord trauma accounts for 70% of the total number of CNS injuries.

Many spinal cord (SCI) patients remain permanently paralyzed with complete or partial loss of neurological functions below the site of injury [2]. The most common is paralysis of the body, usually affecting both lower limbs. At the same time, complications may arise when loss of sensitivity, urinary tract control, or the development of spasticity occur in the affected area [3]. Statistics shows that victims are twice as often men as women, with the highest occurrence of cases between the 19 and 40 years of age [4]. Care for patients with injured spinal cord is demanding and often requires lifelong financial costs [4].

The neurological outcomes depend on the range of damaged neuronal populations at the injury site, the level of disconnection of ascending and descending neuronal pathways, the secondary damage (edema, inflammation, and ischemia), and the age-dependent activation of regenerative processes (endogenous production of trophic factors and revascularization). Thus, patients with incomplete injury who retain some sensory or motor function below the lesion, undergo an extensive rehabilitation program to have a better chance of recovering some function. On the contrary, severe spinal cord injury causes a life-lasting disability for which currently no effective therapy is available. Another important factor is age; statistics shows that younger patients have better prognosis of recovery.

Therefore, the main objective of biomedical research is the development of new therapeutic procedures that would contribute to a more effective functional outcome and improvement of the quality of life.

In this chapter, we would like to highlight pathological consequences that could be evaluated by temporal and spatial proteomic analyses, leading to discrimination of the proteome within the entire spinal cord after acute injury. These data will be correlated with delivery of individual neuroprotective and combinatory neuroregenerative strategies for SCI treatment.

## 2. Pathology

Spinal cord trauma triggers a pathophysiological complex of cellular and molecular reactions leading to edema, hemorrhage, free radical formation, glutamate excitotoxicity, ischemia, macrophage phagocytic activation, glial scar formation, and apoptotic changes in the injured tissue [5]. These processes take place within a few minutes to weeks and years after the injury.

During this time, under the influence of secondary events, small primary damage will spread to the surrounding healthy area within the craniocaudal axis, causing partial or complete loss of physiological functions below the site of injury.

One of the key events of secondary processes is inflammation characterized by fluid accumulation (edema) and the recruitment of immune cells (neutrophils, T-cells, macrophages, and monocytes) [6]. In fact, spinal cord microglial cells normally function as a kind of reactive immune cells that begin to respond to signals after pathological stimuli (injury, infection, or tumors) [7] and are activated at the lesion epicenter [8]. It has been suggested that microglia/macrophages can be polarized into M1-neurotoxic or M2-neuroprotective states and produce a variety of cytokines, chemokines, and neurotrophic factors. However, the mechanisms regulating microglial polarity remain unclear [9].

In addition, not only stimulated microglia/macrophages but also astrocytes, meningeal cells, and fibroblasts together with the increased production of inhibitory chondroitin sulfate proteoglycans (CSPGs) are involved in the spinal cord pathogenesis [10]. Macrophages can alter their phenotypes and functions according to changes in the spinal cord microenvironment during subacute and chronic phases. Thus, SCI triggers an excessive inflammatory response mediated by the invasion of M1/M2 macrophages into and around the central lesion at subacute phase, but not at chronic phase when the formation of glial scar occurs.

### 2.1. Neuroinflammation

In the CNS, immune cells acquire diverse phenotypes depending on the pathophysiology of the microenvironment.

The inflammatory environment of injured spinal cord contains pro-inflammatory cytokines such as tumor necrosis factor $\alpha$ (TNF$\alpha$), interleukins IL-1 and IL -6. Anti-inflammatory molecules, like transforming growth factor $\beta$1 (TGF$\beta$) and IL-10, are released as well. Immune response in the CNS is mediated by resident microglia and astrocytes, which are innate immune cells without direct counterparts in the periphery.

Among glial cells, microglia are firstly activated and are able to play a bifunctional role. They secrete toxic factors and contribute to tissue damage, but at the same time also release neuroprotective and neurotrophic molecules to allow tissue repair [11]. Interestingly, microglia and astrocytes are able to cross-talk with CNS-infiltrating immune cells, such as neutrophils, T cells, and other components of the innate immune system, as well as with neurons.

**Neutrophils** are considered as the first inflammatory cells to arrive at the site of injury with a peak at 24 h after injury [12]. They are rapidly mobilized from the bone marrow in response to signals from pro-inflammatory CXC (CXCL8) family chemokines, IL- and cytokine-induced neutrophil chemoattractant 1 (CINC-1) to mediate pleiotropic functions in the immune-inflammatory response [13]. Neutrophils adhere to post-capillary venules 6–12 h post SCI and afterwards they migrate into the lesion site to phagocytose debris [14]. Neutrophils generate their own cytokines after stimulation by pro-inflammatory mediators and produce proteases

via the NF-kB translocation pathway. Phagocytic activity can induce NF-kB activation [15, 16], and other mediators such as matrix metalloproteases (MMPs), and cytokines TNF$\alpha$, IL-1, IL-8, and TGF-$\beta$ [17].

**Microglia** are a unique myeloid cell population, derived from the yolk sac during a narrow time window during development (before vascularization or definitive hematopoiesis) in the embryo. Microglia cells, present in the CNS parenchyma, are sustained by the proliferation of resident progenitors, independently of blood cells.

Their response following pathological stimuli is characterized by an accumulation at the lesion site and the release of various bioactive molecules. Two categories of molecules are released, some are cytotoxic or pro-inflammatory, and others may aid survival and regeneration. Resident monocytes are the first cell types to respond after injury within 1–2 h, which starts the initial acute inflammatory response accompanied by an expression of TNF$\alpha$ and IL-1 (M1 phenotype). This leads to the recruitment of other immune cells. M1 macrophages promote phagocytosis. Eight hours after injury, the production of pro-inflammatory cytokines is terminated, thus promoting the differentiation of macrophages into an anti-inflammatory M2 phenotype with the expression of arginase 1 and a mannose receptor (CD206). M2 macrophages promote angiogenesis and matrix remodeling, while suppressing destructive immunity [18]. The ratio M1/M2 varies in terms of the microenvironment.

These findings correlate with accumulating evidence pointing to a chronological time line expression of different degeneration- and regeneration-associated genes that are involved in the pathogenesis and endogenous repair or plasticity during days to months following SCI.

### 2.2. Neuro-glial interactions

Microglia activation may be beneficial, deleterious or neutral [8, 9]. Neurons express cell surface glycoproteins (CD22, CD47, CD200, and NCAM) to prevent microglia activation [10, 19]. A relationship between the nervous and immune system has been studied this past decade. Indeed, glial cells (microglia and astrocytes) not only perform supportive and nutritive roles for neurons, but also serve to defend the CNS. On the other hand, excessive and prolonged glial cell activation may result in more severe and chronic neuronal damage, leading to neuroinflammation and neurodegeneration [11, 13].

Neurons are able to control microglia with two types of signals: “On” or “Off” [20]. Off signals (TGF-$\beta$, CD22, CX3CL1, neurotransmitters, and CD20) are found in healthy conditions to maintain homeostasis and also restrict microglial activities under inflammatory conditions to prevent damage to healthy tissue. Conversely, “On” signals [CCL21, CXCL10, and MMP3 (from apoptotic neurons)] are produced by damaged and impaired neurons to activate microglia (pro- or anti-inflammatory) [21].

### 2.3. Glial scar

Glial scar is the accompanying pathological phenomenon of various CNS injuries. The site of injury is infiltrated by macrophages from the bloodstream, fibroblasts, astrocytes, microglia, and oligodendrocytes [8]. Later, precursors of oligodendrocytes and meningeal cells are activated.

Activated astrocytes proliferate and, together with other glial cells, produce a glial scar that encloses the lesion site and prevents the diffusion of ions, neurotransmitters, and other metabolites from damaged tissue into surrounding healthy tissue [22]. This protects undamaged tissue from inflammation and demyelinization, while at the same time, it also prevents regeneration of nerve fibers, which is a serious problem for the treatment of spinal cord injuries. Activated astrocytes reveal thicker projections that intersect with each other and are connected by tight joints. Astrogliosis is accompanied by increased expression of glial fibrillary acidic protein (GFAP), vimentin, and markers for neural precursor cells (Nestin) [23]. In reactive astrocytes, increased synthesis of extracellular matrix protein CSPGs has been reported, which are inhibitory to axon growth itself [23]. Similarly, oligodendroglia, together with meningeal cells migrating into the lesion, form a significant barrier for axonal growth by producing inhibitory molecules (NOGO) and other proteoglycans [24].

### 2.4. Inhibitory molecules

NOGO inhibitory protein [25, 26], myelin glycoprotein oligodendrocyte (OMGP) [27], myelin-associated glycoprotein (MAG) [28] together with secondary inhibitors, including the large group of chondroitin sulfate proteoglycans (CSPGs), are among the major inhibitory molecules that block axonal regeneration [24, 29]. While blocking the penetration of axons, they contribute to the formation of so-called blind clusters, unable to form functional connections with terminal neurons. These pathological formations often cause painful irritable syndrome [30].

Inhibitory CSPGs are synthesized by neurons and glial cells. They play an important role in the physiological development of the CNS, such as cell migration, maturation, differentiation, survival, and tissue homeostasis, but in the case of disruption of tissue homeostasis, increase their expression and consequently inhibit regeneration [31]. These molecules interact extensively with extracellular matrix components [32], for example, with laminin, fibronectin, tenascin, and collagen [33]. Additionally, they bind to growth factors, midkine, pleiotrophin, fibroblast growth factor [34], or inhibitory growth factors such as semaphorins [19] and contribute to the formation of a glial scar that inhibits regeneration of axons [35]. NG2 glycoprotein, which belongs to the most important inhibitors of the CSPGs group, is produced by oligodendrocytes precursor, meningeal cells and macrophages [36]. Accumulation of NG2 was seen at the site of injury, where it blocks regeneration of the axons [31]. Co-expression of NG2 and PDGF-$\alpha$ receptors in the same population of CNS cells confirmed its specific expression in oligodendrocyte precursors [37]. NG2-positive oligodendrocyte precursor cells are often the first cells to respond to injury. Unlike microglia, reactive oligodendrocyte changes are local and occur only in the immediate vicinity of the injury. Previous experiments confirm the initiation of spontaneous regeneration in SCI, as reflected by the incidence of GAP-43-positive axons. They were found in the segments above the lesion at first week [38]. In the central lesion, which forms a mechanical and chemical barrier, the inhibitory proteoglycan NG2 was significantly enhanced [39]. Immunohistochemical analyses using specific NG2/GAP-43 antibody confirmed that increased accumulation of NG2-positive cells at the central injury creates a barrier for successful diffusion and further ingrowth of GAP-43-labeled axonal fibers at acute phase [38]. Sequential administration of ChABC enzyme caused degradation of NG2 glycoprotein, which modified the extracellular matrix and created a tolerant environment for longer term recovery (2–3 weeks).

### 2.5. Neuropathological consequences based on proteomic analyses

Based on the recent analyses of SCI pathological processes, it seems that complex changes in gene and protein expression as well as in cellular interactions are taking place not only at the central lesion but also in adjacent segments. However, the exact mechanisms by which proteins involved during inflammation, recruitment and microglia activation, glial scaring, remyelination, or axonal growth function remain to be further explored [5, 10, 21, 35]. Therefore, understanding of the molecular cross-talk occurring between cells at the lesion site and in the adjacent segments needs to be further investigated [21]. In particular, studies that are able to take into account both spatial and temporal data may identify interesting molecular targets [40]. Such an investigation could be performed by a **proteomics approach**, which can be connected to cellular and physiological studies as well as to a global regeneration-activated gene (RAG) investigation. Mass spectrometry (MS) plays a central role among proteomics approaches. Several developments allow fast identification of lower abundance proteins such as cytokines and chemokines [41]. Furthermore, MS is highly used in neuroscience to discover biomarker candidates and also to study the differential expression of proteins at any given time in a proteome and they are then compared with the pattern of those from healthy ones.

Thus, to better understand the pathology based on secondary injury processes and plasticity, it is necessary to analyze entire spinal cord tissues in time, thus collecting tissues from the epicenter and both adjacent segments above (rostral) and below (caudal) the lesion firstly in acute, and afterwards in chronic SCI experimental models, expecting the release of different molecules. They will most likely reflect pathology *in situ*, at each specific segment, which may contribute to the final view of ascending or descending pathway disruption resulting in aggravation of clinical symptoms [41].

Nowadays, we can count on innovative proteomics technologies that can screen, identify image lipids and peptides in each spinal cord segment-derived conditioned medium (CM), or in the spinal cord tissue obtained *in vitro*, to better understand protein composition changes along the rostro-caudal axis after SCI with time in SCI.

Recently, application of shotgun proteomic analysis and label-free quantification to conditioned medium from the injured spinal cord (CM) identified chemokines (CXCL1; CXCL2; CXCL7, CCL2, CCL3, CCL22, CLCF1, and EMAP II) and neurotrophic factors (TGF, FGF-1, PDGF, and FGF1) in the lesion and rostral segments. These molecules are known to have immune-modulator and neurotrophic properties and ability to polarize macrophages/microglial cells into the M2 phenotype [10].

Chemokines are the most important molecules released immediately after SCI. Specific chemokines (CXCL1, CXCL2, CXCL3, CXCL5, CXCL7, CCL3, CCL20, and IL6) that are secreted by macrophages or epithelial cells after injury have the ability to attract neutrophils and lymphocytes, activate inflammation and stimulate extracellular matrix synthesis and tissue remodeling. Recent data showed that the cytokine profile changes in time between the segment above and below the lesion. This is in line with the hypothesis that immune cells that are attracted along the spinal cord upon injury insult are quite different between rostral (R1) and caudal (C1) segments in time. Recently, using proteomic analysis it has been documented that specific immune cells initially migrate toward R1 and then C1 segment [41]. In line with this,

IL6 and CCL20, which are known to attract T regulator lymphocytes through CCR6 binding, were expressed firstly in R1 at 3 days after SCI and secondly appeared in C1 at 7 days [40]. Furthermore, results from proteomic analysis were re-confirmed with cytokine/chemokine arrays and correlated with immunohistochemistry for neutrophils and Tregs. These experiments confirmed that neutrophils were abundantly detected in both R1 and C1 segments with a peak reached 3 days after SCI without any differences in terms of amount between each segment. However, their level decreased in time. In comparison, Tregs were present 3 days after SCI, in higher amounts in the rostral segment than in the caudal one. Their levels peak at 7 days for both segments and then decrease at 10 days [40]. These data are in line with the presence of CXCL1, CXCL3, CXCL5, CCL20, TIMP-1, and IL6 in R1 at 3 days, which are known to attract neutrophils and lymphocytes. In C1, a delay was observed in the recruitment of the Tregs, which were detected 7 days after SCI and correlated with the detection of CCL20 in C1 only at 7 days, whereas neutrophils and microglial cells were already present at 3 days [40]. Taken together, the results showed that C1 is clearly different from R1 in terms of cell types and molecular content in a time course manner, and is revealed to be a target segment for therapy.

The functionality of chemokine released from injured spinal cord tissue can be evaluated by chemotaxis assay, thus investigating the BV2 (microglial) cells activation, followed by Western blot, and M1/M2 polarization through CX3CR1 and CD206 expression.

*In vitro* chemotaxis assays confirmed that BV2 cells were highly responsive to the cytokine cocktail present in the CM from lesion and rostral sites, compared to CM from the caudal site after SCI. Interestingly, the BV2 migratory potency induced by CM derived from rostral and lesion segments was 37-fold higher compared to the ATP or LPS stimulations that increase their migration by close to 3-fold, due to the specific factors found in the complex CM [41, 42]. Furthermore, immunocytochemical studies prove that activated BV2 cells exposed to CM from the rostral segment overexpressed the CX3CR1 receptor, known to correspond with the M2 profile. This finding was strengthened by Western blot analysis and lack of labeling with C2KR, an M1 receptor [41]. These data together with *in vivo* CX3CR1 expression were in close coherence with published transcriptomic experiments showing that in the injured spinal cord, M2 gene expression is transiently expressed during 7 days after injury, while the M1 gene expression is maintained for up to 1 month [43].

Spatio-temporal proteomic analysis of spinal cord tissue between 3 and 10 days after injury provide clear evidence of regionalization between the rostral and caudal axes, with an expression of neurotrophic and immune modulatory factors in the rostral region, in contrast to inflammatory and apoptotic molecules in the caudal region.

Neutrophic factors were found at 3 and 7 days after injury and disappeared at 10 days. They were replaced by synaptogenesis factors reflecting the fact that a neurorepair process is taking place in the rostral segment after 10 days. In fact, more neurotrophic factors have been detected in the lesion and rostral parts, i.e., CTGF (connective tissue growth factor), NOV (Protein NOV homolog), PIGF (placenta growth factor), FGF-1 (fibroblast growth factor 1), BMP 2 or BMP3 (bone morphogenetic proteins (2 or 3), NGF, PGF, TGF beta (1–3) (transforming growth factor beta), periostin, GAP-43, neurotrimin, neurofascin, and hepatocyte growth factor-regulated tyrosine kinase substrate (HGS). In addition, molecules involved in neuronal development/differentiation/neuronal migration, i.e., CRIP1 (cysteine-rich protein 1), DRP-5 (dihydropyrimidinase-related

protein 5), Negr1 (neuronal growth regulator 1), NCAN (neurocan core protein), CD44, Wnt8, syndecan-4, nexin, and Bcl-2, were identified. Specific factors involved in immune cell chemotaxis or cellular adhesion, including complement factors (C1qb, C1qc, factor D, factor I, and CD59), tetraspanins (CD9 and CD82), and CD14 have also been characterized [40, 41].

In contrast, proteins produced in the caudal region were related to necrosis factors (BAX, BAD, Caspase 6, and neogenin), cytoskeleton proteins, synaptic vesicle exocytosis, chemoattractant factors, and neuronal postsynaptic density.

These data are in line with our previous *in vivo* results demonstrating that neurite outgrowth takes place from rostral to lesion but never in the opposite direction from caudal to the lesion. Furthermore, the presence of chemokines, lectins, and growth factors in the rostral but not in the caudal segment clearly document the immediate inflammatory response together with activity-dependent factors released by neurons and glia.

In order to investigate the neurotrophic role of CM derived from the injured tissue, studies testing neurite outgrowth in rat DRG explants have been undertaken. Data from these experiments confirmed that enhanced neurite sprouting of DRGs facilitated by CM from rostral and lesion segments were most likely mediated by the content of neurotrophic factors, i.e., FGF-1, NGF, PGF, BMP 2 or BMP3, GAP-43, neurotrimin, neurofascin, and other molecules involved in neuronal development/differentiation/migration. Although the principal role of NGF/TrkA pathways in sensory axon outgrowth has been widely demonstrated, other neurotrophic factors including the BMPs (members of the TGFβ superfamily) or GAP-43 have to be taken into account [41, 44].

In summary, it has been demonstrated that few days after SCI, a clear regionalization occurs between the rostral and caudal axes, with expression of neurotrophic and immunomodulatory factors in the rostral region, in contrast to inflammatory and apoptotic molecules in the caudal region. These data indicate the importance of stimulating neurite sprouting at segments below the lesion by inhibiting inflammation and turning polarization of M1 cells to the M2 state, which could have a clear impact on neurorepair. Therefore, these findings should be taken into account when planning new treatment strategies.

## 3. Neuroprotection in the CNS

Neuroprotection is defined as a curative strategy against harmful biochemical and molecular lesions that, if left untreated, lead to CNS damage [29]. The main purpose is to protect the damaged area by modifying the pathophysiological cascade with the limitation of harmful processes at secondary damage. In particular, the objective is to save those cell populations that are not directly affected by the injury, but due to secondary processes will underlay delayed apoptosis [45, 46]. In this regard, the primary goal is to suppress secondary inflammatory processes, edema and hemorrhage, and excitotoxicity that expand from the lesion center above and below the lesion site and acts destructively on healthy cells. Neuroprotection is among the specific therapies used in CNS injuries [47].

One of the important concepts that have recently resonated is the use of neuroprotective strategies that are applied to the spinal cord in conjunction with clinically proven operative methods

of decompression and reconstruction of the spine. This clearly indicates that early intervention on traumatic spinal cord injuries can significantly affect the prognosis of the disease [3]. Therefore, great attention has been paid to studies that deal with the optimal timing of surgical procedures for acute spinal cord injury [48]. Previous data suggest that patients undergoing surgical decompression within 24 h after spinal cord injury have a significantly better recovery prognosis [29]. Currently, a number of innovative neuroprotective strategies for acute spinal cord injuries are being tested and evaluated in randomized controlled trials. Experimental studies on animal models showing promising results, such as ChABC, minocycline, riluzole, granulocyte colony stimulating factor (G-CSF), are now being tested in clinical studies [2, 49]. Hypothermia induced by intravascular cooling infusion administered epidural or subcutaneously has achieved success during acute SCI treatment.

### 3.1. Pharmacotherapy

Pharmacotherapy is one of the most widespread forms of treating secondary damage that use a wide variety of different types of molecules to target specific secondary processes. These are comprised of anti-inflammatory or neurostimulating compounds such as, minocycline, neurotrophic factors (BDNF, GDNF, NGF, and erythropoietin), and molecules that alleviate regenerating axons from the inhibitory effects of extracellular matrix molecules.

In particular, chondroitinase ABC eliminate CSPG with the major component NG2 which inhibits the regeneration of damaged axons [50]. Nogo-neutralizing antibodies or blockers of the post-receptors components RhoA, are used to improve long-distance axon regeneration and sprouting [25]. Previous studies have identified Rho pathway as important to control the neuronal response after CNS injury. Therefore, a drug called Cethrin® that blocks activation of Rho is actually in phase I/IIa of clinical trials [48]. The most encouraging findings were observed in patients with cervical SCI, whereas patients with injuries at thoracic level received only modest neurological recovery. Although the patient numbers were small in this trial, the results obtained indicate some evidence of efficacy to enhance functional recovery and warrant further clinical trials [51].

### 3.2. Molecular therapies: chondroitinase ABC, minocycline, tacrolimus, riluzole

**Chondroitinase ABC** is a bacterial enzyme that reduces the inhibitory effect of CSPGs at the site of injury. In order to increase CNS regeneration, only chondroitinase ABC purified from Proteus vulgaris [52] should be delivered. The mechanism of action lies in removing GAG chains from the nuclear protein and converting them to unsaturated disaccharides [34]. These stimulate the release of growth factors and proteins attached to GAGs of CSPGs, thereby enabling their diffusion and interaction with neural cell receptors. ChABC has been shown to promote neuroprotection and neuroregeneration [53]. Experimental administration of ChABC after cervical SCI positively affects the branching of damaged and intact descending pathways around which increased accumulation of CSPGs and then inhibition of axonal growth occurs. The neuroprotective effect of ChABC has been described also for the hemisection of the spinal cord [50, 54], transection of dorsal columns [55], and after compression injury of the thoracic spinal cord and the peripheral nerve [56] or in adult rats with visual deficits [57].ChABC administration is often

combined with other therapeutic elements such as LiCl or Schwann cell transplantation [58] that can trigger regeneration. On the other hand, axonal plasticity supported by histological analyses did not correlate with motor function improvements of hind limbs. A similar conclusion was obtained by a group led by Cafferty [59]. There are several explanations for the negative correlation between the growths of axons without functional enhancements.

*3.2.1. Orientation and quantity of functional synaptic connections*

Functional recovery is dependent on correct orientation of axons and their functional links to the target structure. In some studies, linearly oriented as well as disordered nerve fibers that regrow through the lesion in different directions have been observed. Theoretically, they might increase the plasticity of tissues, because they cover a broader area. On the other hand, disorganized nerve fibers are often losing functional links with the target structure [60].

*3.2.2. The time required for the maturation of functional linkages*

Another possible negative factor that influenced clinical outcome may be the short-term survival of experimental animals required for functional contact formations. The intensive regeneration process in human patients progresses for months or years, and it is therefore necessary to prolong the length of survival in experimental animals from 3 to 6 months.

*3.2.3. Method of ChABC administration*

The important factors that affect the efficiency of ChABC therapy are: (i) method of local delivery, (ii) dose, (iii) timing of therapy, and (iv) efficacy of ChABC, since it is a bacterial enzyme which loses its activity *in vivo*. Therefore, to ensure its activity, repeated intrathecal delivery of ChABC or thermostable ChABC should be considered.

The undesirable effects of ChABC delivery have been observed only in rare cases. They are often related to the immune response against the enzyme or to neoepitopes (cleavage products) that this bacterial enzyme forms. Despite the rare negative effects, ChABC broadly reorganizes extracellular matrix, changes cell adhesion and tissue diffusion, and stimulates the functional recovery of damaged CNS [38].

In summary, the results confirmed that early reduction of NG2 allows extracellular matrix reorganization, creating a favorable environment for the initial neuroprotective processes to enable significant regrowth of injured axons in the epicenter of damage. Experimental studies also demonstrate that in order to achieve a better neurological outcome, ChABC needs to be combined with other therapeutic approaches. These may increase the plasticity of the injured tissue, create an environment for the axon outgrowth of fibers, and navigate these fibers to the right direction for the creation of fully functional synaptic connections.

**Minocycline** is a second-generation, semisynthetic tetracycline that has been commonly used in the treatment of acne vulgaris in children, because of its antibiotic properties against both gram-positive and gram-negative bacteria. However, it has been shown that minocycline can exert a variety of biological actions that are independent of their anti-microbial activity, including anti-inflammatory and anti-apoptotic activities, inhibition of proteolysis, angiogenesis, and tumor metastasis. Minocycline reveals high lipid solubility [61] and therefore easily

crosses the blood–brain barrier [62]. This drug has been shown to be beneficial in various experimental animal models of CNS diseases. Primary mechanisms of action lie on the inhibition of microglia activation, which would justify its potential effectiveness in the treatment of neuroinflammatory and/or neurodegenerative disorders [63]. Different *in vitro* studies have described minocycline's ability to block LPS-stimulated inflammatory cytokine secretion and Toll-like-receptor (TLR)-2 surface expression in the BV-2 cell line and on primary microglia isolated from the brains of adult mice. Minocycline also attenuated the mRNA expression of inflammatory genes, including IL-6, IL-1β, major histocompatibility complex (MHC) II, and TLR-2. In experimental models of SCI, minocycline delivery significantly improved the function and strength of both hindlimbs, reduced the gross lesion size in the spinal cord, and enhanced axonal sparing. Minocycline-treated rats showed decreased release of cytochrome c from the mitochondria, resulting in markedly enhanced long-term hindlimb locomotion [64]. In traumatic SCI, results [65] showed that both short and long-term treatment with minocycline had a neuroprotective effect on the spinal cord segments located rostral to the injury epicenter. Minocycline has also been shown to improve functional recovery after SCI through the inhibition of pro-nerve growth factor production by microglia, thereby reducing oligodendrocyte death and apoptosis after traumatic SCI. It has been shown to inhibit the expression of p75 neurotrophin receptor and the activation of the Ras homolog gene family, member A (RhoA) after SCI [61]. Furthermore, previous study reported that minocycline might also exert a neuroprotective effect in SCI by inhibiting caspase expression and matrix metalloproteinases [65]. Metalloproteinases belong to a group of proteases that are responsible for the degradation and remodeling of the individual components of the intracellular matrix in normal tissue, and their activity is regulated by endogenous inhibitors. However, many pathological CNS conditions are characterized by increased metalloproteinase activity due to the reduced activity of their tissue inhibitors. The imbalance between intracellular matrix metalloproteinases and their inhibitors may lead to destructive proteolytic damage to the CNS tissue [45]. Minocycline has shown beneficial effects in many experimental studies [65] and was therefore also approved for phase I and II clinical trials in patients with completely injured spinal cord. The overall results confirmed the safety of the drug, but did not show improved motor outcomes in patients treated with minocycline compared to placebo. However, in a subset of patients with incomplete spinal cord injuries, patients experienced significant improvement [66]. Based on this promising outcome, a Phase III clinical trial was initiated in patients with acute spinal cord injury. This is currently ongoing and will be completed in 2018 [67].

Another interesting formulation is **FK506** (tacrolimus) isolated from the bacterium *Streptomyces tsukubaensis*, which presents a potent immunosuppressive drug. Primarily, it is used to reduce allograft rejection in organ transplantation, but also offers neuroprotective properties for central nervous system trauma. FK506 blocks the activation of calcineurin through the formation of complexes with immunophilins. However, it binds to a different immunophilin than cyclosporine A (CsA) [68]. FK506 has been found to increase nerve regeneration and functional re-innervation after peripheral nerve injury, as well as prevent axonal damage in toxic neuropathies [69]. Several studies document that FK506 delivery protects tissue from secondary injury and showed a beneficial effect during an acute SCI [70]. However, long-term administration of FK506 after experimental spinal cord injury in rats has shown to be not as effective [71]. FK506 was also used as a potent inhibitor of activated T-cells that infiltrates the injured spinal cord. Thus, it can modulate inflammation and ameliorate neuroprotection through its immunosuppressive

action on immune cells [72]. Furthermore, the immunosuppressive action of FK506 was proven by the prevention of graft rejection following spinal cord ischemia and SCI [44].

**Riluzole** is commonly used in the treatment of amyotrophic lateral sclerosis (ALS) to protect against nerve cell degeneration. The possible mechanism of action of riluzole is blocking sodium channels as well as glutamate excitotoxicity. The deleterious effect of glutamate overproduction during CNS damage can be reduced by both reducing the synthesis and preventing its release into the synaptic cleft. In the case of riluzole, its mechanism of action is most likely thought to be the reduction of glutamate synthesis and thereby its release into the presynaptic region of the neuron. In a recent study, 155 patients were randomized to riluzole treatment (100 mg/day) or to placebo. The patients were monitored for 12–21 months [48]. Survival was significantly longer in the riluzole-treated group compared to placebo-treated patients. The median survival time was 17.7 months for riluzole compared to 14.9 months for placebo [4]. Additionally, there was a significant improvement in motor function in patients with cervical SCI receiving 50 mg riluzole twice a day for 14 days after injury, compared to the control group [73].

## 4. Regeneration

Regenerative medicine is a dynamically developing area of medicine whose mission is to restore damaged tissue. Although different tissues and organs have different recovery capabilities, there are diseases and CNS injuries that have limited regeneration and, unfortunately, they cannot be treated by conventional therapies. One of the innovative regenerative medicinal approaches is the use of stem cells and biomaterial-based treatments in order to replace damaged tissue or to supplement missing trophic factors in various CNS diseases [3].

The twenty-first century resonates with the rapid development of regenerative medicine, where methods of isolation and processing of stem cells and the use of highly compatible biodegradable materials and nanotechnologies directed to the treatment of SCI patients has been improved [74]. However, successful cell therapy is influenced by various factors such as: (i) selection and processing of stem cells (adult, induced pluripotent stem cells), (ii) delivery strategies (local, systemic), (iii) dosage (single, continuous), and (iv) appropriate timing of administration (acute, chronic phase of SCI). Selection of stem cells is important for their compatibility with host tissue. For this reason, in clinical studies, stem cells obtained from the tissues of the patient are preferred. Autologous stem cell transplantation obtained from the bone marrow and adipose tissue of a patient is used in the treatment of hematopoietic diseases, in the regeneration of bone tissue and cartilage, and possibly also in spinal trauma [74]. At present, an autologous transplantation of the so-called induced pluripotent stem cells (iPKB) derived from adult somatic cell patients has also been considered. By new procedures, we can reprogram a fully differentiated somatic cell (fibroblast) toward a cell with primitive pluripotent origin that is derived into the desired cell population [75]. In other cases, allogenic stem cells that meet the compatibility criteria (ABO, HLA) may still be used, but patients must still receive immunosuppressive therapy for a lifetime. In addition, stem cells are a major tool for gene therapy when they can produce some trophic factors and other molecules that are necessary for the regeneration of injured nerve tissue.

Among different **mono-therapies**, more **complex cellular therapy** has reached considerable attention due to targeting multiple aims, such as bridging the cavities or cysts, replacing dead cells, and creating a favorable environment allowing axonal regeneration [76].

### 4.1. Regenerative approaches toward biomaterials

SCI results in cysts or cavities at the site of the lesion, which gradually expand in the caudal direction. From this point of view, cell therapy alone for such a progressive pathological process as SCI is insufficient. Therefore, it is recommended to combine the administration of stem cells with biodegradable biomaterials that fill the cavities. The main objective is to optimize mechanical properties, cell adhesion, and biodegradability of synthetic or natural materials and develop new methods to deliver cells to the lesion site. One of the most important features for the successful integration of the implant into damaged tissue of the spinal cord is its optimal mechanical strength. If the biomaterial is too rigid, it can cause compression of regenerating axons and the formation of additional secondary cavities between the implant and surrounding spinal tissue. Therefore, it is preferable to use an injectable biomaterial that can properly adapt to the lesion [63, 77].The stem cells with which the implant should colonize also require the presence of growth factors that help them to survive in the unfavorable environment of the injured spinal cord. Chen and his scientific group compared the regenerative capabilities of several biodegradable multichannel biomaterials with different mechanical properties that were colonized by Schwann cells and implanted into the spinal cord after transection [63]. Compared to the poly-caprolactone fumarate material, which had significantly higher compression modulus values, biomaterials based on hydrogels showed significantly smaller cavities and promoted material vascularization and Schwann cell infiltration [63].

The biomaterial has to be biocompatible; this depends on the properties of the surface of the material and its interactions with cells or proteins [78]. However, we have to be aware of non-specific inflammatory responses of the recipient to the foreign biomaterial, and its extent determines the rate of implant biocompatibility. Interestingly, the acute response of the immune system that is mediated by macrophages or dendritic cells can be neuroprotective and can promote CNS regeneration. Modulation of the inflammatory response by the type of biomaterial surface can therefore be an auxiliary tool for repair mechanisms of the tissue. In principle, the physical properties of biomaterials should simulate the extracellular environment of the central nervous system and thereby ensure the diffusion of neurotrophic factors. Interactions between biomaterial surface and living tissue are usually mediated by a layer of proteins. Most biomaterials have an optimized surface with bioactive molecules or oligopeptide sequences [77]. This guarantees the adhesion of specific cells or their parts (e.g., axons).

**Biodegradable** materials are more desirable than non-degradable ones. Their degradation is most often mediated by hydrolysis and enzymatic cleavage. The rate of degradation can be controlled by various factors, such as molecular weight and polymer structure, crosslinking, and use of copolymers [79]. Of course, degradation products must not cause any immune response and the rate of breakdown of the material must be appropriate to the formation of new tissue. Biomaterials that are used to regenerate nerve tissue usually degrade for weeks or months, depending on the axonal and vascular material growth. Degradation can take place by gradual erosion of the surface of the material while maintaining the structural integrity of the material

or by the gradual breakdown of the material structures. The first method is more advantageous because the collapse of the material may stop the regeneration process.

**Alginate materials** are natural and have a significant role because most of them are biodegradable. This group of natural materials also includes collagen, methylcellulose, or hyaluronic acid-based materials. The disadvantage is their natural variability and the risk of immunogenicity. The implantation of lyophilized alginate into the cavity of newborn or young rats stimulated the growth of non-myelinated and myelinated fibers in the hydrogel [80], as well as the formation of functional neuronal connections that have been demonstrated. In another study, the optimal combination of EGF and bFGF was chosen routinely in conventional 2D cultures in order to obtain the desired amount of proliferating cells. The goal was to create a strong but reversible binding of both factors to alginate-sulfate [81], allowing their prolonged and sustained local presentation to neural progenitors in cell culture. This develops an active biomaterial that eliminates the need for external continuous growth factor substitution during cell culture. However, it is crucial to determine the optimal concentration of growth factors that could mimic similar concentrations of bFGF/EGF commonly used in the 2D system culture (10–20 ng/ml for each factor/3 days). In this case, the equilibrium binding constant of the selected factors on alginate-sulfate plays an important role. The initial concentration of both bFGF and EGF factors (200 ng) was shown to be sufficient for their continuous release over 21-day incubation [82]. The concentration of growth factors released within the first week *in vitro* initiated cell proliferation and the formation of typical 3D neurospheres. Consequently, there was a decline in the growth factor concentrations; the cells migrated from the neurosphere and differentiated to neurons, astrocytes and oligodendrocytes. These results confirmed that the 3D alginate biomaterial, which gradually released growth factors, creates optimal conditions for long-term survival and differentiation of neural progenitors *in vitro* [82].

The developed 3D biomaterial was implanted locally into SCI rats. The results confirmed that the optimal bioavailability of growth factors (EGF and bFGF) from the implant stimulated neuroregenerative processes. Enhanced sparing of spinal cord tissue and increased number of surviving neurons (ChAT-cholinacetyltransferase-positive neurons), corticospinal fibers (BDA-labeled), and blood vessels at the site of injury [83] occurred. Inflammatory processes were partially suppressed, but not astrogliosis. These partial results indicate the possible use of active alginate biomaterials enriched with bioactive molecules in the treatment of CNS trauma [83].

Although the biomaterials themselves can affect nerve tissue regeneration by creating a space for cell growth through the lesion, it is increasingly clear that combined therapy has a synergistic effect and leads to better results. Therefore, biomaterials are most often combined with different types of cells or enzymes digesting proteoglycans in glial scars, as known for chondroitinase ABC. The most commonly used cells are MSC, Schwann cells, and neural stem cells that can express Noggin, promoting neurogenesis and suppressing gliogenesis [84]. Biomaterials can also serve to release the biologically active substance, which can then create a gradient that promotes cell growth into the implant. Biologically active agents may be growth factors (EGF, FGF), cytokines, neurotrophins (NT3, NGF, BDNF, and GDNF), neurotransmitters, and anti-axon growth inhibitory antibodies [85].

In conclusion, it is necessary to combine these strategies to further enhance the final effect.

## Acknowledgements

Supported by APVV 15-0613, ERANET- AxonRepair, INSERM U1003, VEGA 2/0125/15, SK-FR-2015-0018/ Stefanik, EU SF ITMS 26240220008.

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Chapter 2

# Pharmacological and Nonpharmacological Therapeutic Strategies Based on the Pathophysiology of Acute and Chronic Spinal Cord Injury

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72781

**Abstract**

Spinal cord injury (SCI) induces a series of anatomic and physiological disorders which have severe repercussions on neural function. SCI is classified chronologically into an acute (primary and secondary phase) and a chronic phase. The primary phase results directly from the initial trauma and is comprised of disturbances in neural tissue (mainly axons), blood vessels, and spinal shock. Secondary injury results from a series of time-dependent pathophysiological changes, beginning in the first minutes after SCI and lasting days and weeks. This phase is characterized by biochemical and immunological alterations in the injury site and periphery, leading to neuronal over-excitation, apoptosis, and axonal demyelination. In chronic stages, the pathophysiology consists of disturbances in fiber organization, oligodendrocyte apoptosis, fibroglial scar formation, and cyst formation, leading to parenchymal alterations such as syringomyelia and hydromyelia hindering the possibility for functional basal axonal regeneration. This chapter will review a wide range of pharmacological and nonpharmacological therapeutic strategies in preclinical and clinical phases, each targeting different pathological mechanisms of SCI in acute and chronic stages of SCI; taking into account limitations, advances, scope, and new trends. The chapter focuses on the general aspects of SCI pathophysiology, pharmacological and nonpharmacological treatments acute and chronic stages of SCI.

**Keywords:** spinal cord injury, pharmacological strategies, nonpharmacological strategies, therapeutic, acute and chronic

## 1. Introduction

The spinal cord (SC) has three major functions in human beings: sensibility, autonomous control, and motor control. Destructive mechanisms following SCI can have grave consequences on these functions [1, 2].

Traumatic SCI can originate devastating consequences on patients and those close to them, requiring a great number of lifestyle adjustments. This injury results most commonly from vehicular accidents, falls, and sports injuries, among other traumatic accidents. According to the World Health Organization (WHO), there are approximately between 250,000 and 500,000 cases of SCI per year. Among these, 90% are traumatic in nature with an increased mortality risk within the first year [3].

The pathophysiology of SCI can be divided into primary and secondary damage based on the self-destructive mechanisms following initial injury. These mechanisms can be further divided into three phases according to their temporality: acute, subacute, and chronic phase. The acute phase is characterized by ionic changes, which interrupt nerve impulses and lead to edema; the subacute phase involves a series of events including ischemia, vasospasm, thrombosis, inflammatory response, free radicals (FR) production, lipid peroxidation (LP), and the activation of autoimmune responses resulting in apoptosis. In the chronic phase, all the auto destructive mechanisms generated during the acute and subacute phase increase and demyelination processes are triggered, alongside the formation of a glial scar, which hinders axonal regeneration [4–6].

The objective of this chapter is to review a wide range of pharmacological and nonpharmacological therapeutic options, each targeting different pathological mechanisms in the different time phases of SCI.

## 2. SCI pathophysiology

### 2.1. Acute and subacute phases

Primary damage occurs mechanically at the moment of injury, leading to irreversible sequelae. There are three main mechanisms of injury:

**a.** Contusion in the SC without visible loss of its morphology producing a necrotic zone at the impact site, which mainly affects the dorsal region of the SC.

**b.** Laceration or transection, which results from the penetration of the SC or extreme trauma, and affects SC conduction depending on whether the tissue is partly or completely transacted.

**c.** Compression caused by fractures in the vertebral column, which limit irrigation and can occur without injuring the surrounding ligaments, resulting in ischemic damage in the area where the blood flow was interrupted [3, 5, 6].

Mechanical trauma initially tends to damage primarily gray central matter with a relative preservation of peripheral white matter. Irreversible damage to the gray matter occurs during the first hour after injury, with the same happening to white matter within the first 72 hours [5]. As a result of the mechanical injury, superficial vessels undergo vasospasm, originating an intraparenchymal hemorrhage, which damages the microvasculature of the gray matter [7]. This in turn leads to the decreased perfusion and local infarcts due to hypoxia and ischemia, depending on the severity of the lesion. Furthermore, these can be aggravated by neurogenic or hemorrhagic shock, arterial hypotension, bradycardia, arrhythmias, and intraparenchymal hemorrhage. Therefore, the damage initiated by mechanical trauma has a maximum extension from the third to fifth day after injury, extending from the rostral and caudal segments to the epicenter of the lesion, and affecting both gray and white matter. The main consequence of hemorrhage is neuronal death by necrosis, which is observed primarily in the gray matter [7–9].

The primary lesion causes the rupture of the blood brain barrier (BBB) at the injury site, leading to a focal destruction of neural tissue, which destabilizes neural and endothelial membranes [10]. This phenomenon results in the death of neurons in the hours following SCI, and is associated with edema, negatively impacting blood flow to the SC, thus extending the inflammatory response [11]. Therefore, primary injury gives rise to the cellular and molecular processes characteristic of the secondary injury stage, which promotes neuronal death and alter genetic expression patterns [12].

Autodestructive mechanisms triggered after SCI can persist with time, and thus be found in acute, subacute, or chronic phases. The acute and subacute phases are characterized by the following mechanisms:

#### *2.1.1. Ionic deregulation*

The first secondary mechanism appearing after SCI, ionic deregulation results from an increase intracellular $Na^+$ and $Ca^{2+}$ concentration and a decrease of $K^+$ and $Mg^{2+}$ ions. This results in the depolarization of neuronal membranes, decreased number of ionic channels, and increased transportation of water molecules associated with $Na^+$ and $Ca^{2+}$ ions, leading to edema [13].

#### *2.1.2. Edema*

Vasogenic edema initially appears as a consequence of the BBB rupture, and is further propagated by the loss of ionic regulation, giving way to water accumulation in extracellular spaces. Water accumulation is strongly related to the intensity of the initial trauma [14]. The presence of edema in any part of the CNS results in the compression of adjacent tissue, which leads to ischemia and promotes the development of other self-destructive mechanisms, such as the release of FR, LP, and inflammation [1, 14].

#### *2.1.3. Excessive release of intracellular calcium*

Once the lesion occurs, partial or total loss of the cellular membrane in neurons and axons is triggered, resulting in the depolarization due to the entrance of high concentrations of $Ca^{2+}$ [13].

The resulting ionic unbalance and edema contribute to the massive entry of $Ca^{2+}$, which is intrinsically related to neurotoxicity by the exaggerated release of glutamate and the activation of proteases and phospholipases. This activation triggers the destruction of neurofilaments and the destabilization of key proteins for cellular support, favoring axonal collapse, and fragmentation in the first hours or days post-trauma [15]. In addition to phospholipase activation, the increase in $Ca^{2+}$ contributes to the production of pro-inflammatory molecules, such as arachidonic acid, leukotriene, and thromboxane due to the release of fatty acids from membrane phospholipids [4]. Likewise, intracellular mobilization of cytosolic $Ca^{2+}$ generates reactive oxygen species (ROS), energetic failure, cytoskeletal damage, and errors in protein folding [16].

The sudden entry of intracellular $Ca^{2+}$ likewise leads to the aforementioned glutamate excitotoxicity. These mechanisms conjointly contribute to immediate cell death or the activation of calcium-dependent signaling pathways, which result in cellular death [15, 17].

### *2.1.4. Glutamate excitotoxicity*

SCI affects the regular equilibrium of glutamate and aspartate in the CNS, leading to significant alterations. Fifteen minutes after SCI, glutamate concentration increases to concentrations six times higher than physiological levels [18]. This increase is due to the overstimulation of ionotropic glutamate receptors (GluRs), provoked by the massive entry of $Ca^{2+}$ and $Na^{+}$. This ion flow can induce a secondary increase of intracellular $Ca^{2+}$, leading to an overstimulation of viable neurons and neuronal death. This toxic effect, known as excitotoxicity [19], leads to neuronal and oligodendrocytic death [18, 20].

This phenomenon is mainly evidenced in glial cells, with axonal-myelinating oligodendrocytes showing greater susceptibility. Excitotoxicity signals are regulated by 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate type GluRs; their overactivation facilitates oligodendrocyte death and consequent demyelination after SCI [21].

### *2.1.5. FR production*

Microvascular disruption, ionic deregulation, glutamate increase, mitochondrial dysfunction, and the activation of inflammatory mechanisms stimulate the formation of FR [4, 6, 22]. The cascade of FR production begins with intracellular $Ca^{2+}$ elevation and the production of uncoupled electrons, which bind to $O_2$ molecules, transforming them into superoxide radicals ($O_2^{-}$) capable of increasing oxidative damage by promoting further FR formation [23].

Damage induced by FR, denominated oxidative stress or nitrosative stress, occurs when excessive amounts of ROS and reactive nitrogen species (RNS) are produced, along with low levels of antioxidant defenses. FR production following SCI can damage cellular lipids, proteins, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA), causing mutations or irreversible damage, which leads to cellular death [24]. Moreover, peroxidase (Prx) 1/6 and manganese superoxide dismutase (MnSOD) are modified by phosphorylation, oxidation, or nitration during oxidative stress after injury, inhibiting their antioxidant functions [25].

### *2.1.6. Lipid peroxidation*

One of the most important pathophysiological mechanisms derived from FR production is LP. ROS such as hydroxyl radicals (OH) and $O_2^-$, combine with nitric oxide (NO) to form the superoxidant agent peroxynitrite (ONOO). These reactants, in turn, can protonate at a physiological pH level, forming peroxynitrous acid (ONOOH) [23, 26].

At a physiological pH, ONOO reacts with polyunsaturated fatty acids (PUFAs), taking one electron to form a lipid radical (L•) that interacts with molecular oxygen to form peroxyl lipid radicals (LOO•). Without regulatory mechanisms, LP will result in membrane depolarization and ensuing demyelination in the SC [26, 27]. Substantial damage induced by FR involves an oxidative attack to the cellular membrane, which is made of PUFAs (arachidonic acid, linoleic acid, eicosapentaenoic acid, or docosahexaenoic acid) [28, 29]. Two aldehydic products arise from LP: 4-hidroxynonenal (4-HNE) y 2-propenal (acrolein). These molecules have been characterized in SCI models, forming covalent bonds with basic amino acids found in cellular proteins, and thus altering their structure and functional properties [28].

Likewise, the inflammatory response is partially responsible for FR production after SCI due to its stimulation of NO production. This molecule is produced by different cellular types after SCI and is capable of damaging medullar parenchyma when produced by inducible nitric oxide synthase (iNOS) [29]. High concentrations of NO, which are mainly produced by iNOS, require an immunological/inflammatory stimulus, such as inflammatory cytokines (IL-6, IL-1, and IFN-$\gamma$), resulting in nanomolar quantities produced for prolonged time periods [30, 31].

After SCI, high concentrations of NO (produced by iNOS) and peroxynitrite increase up to three or five times, reaching their peak 12 hours after injury [32]. Some studies have detected iNOS activity 3, 4, 24, and 72 hours following SCI, vinculating its presence to LP, and neural destruction [31–33]. High concentrations of NO simultaneously participate in cellular damage and increase vascular permeability. Consequently, NO contributes to the formation of edema, as well as excitotoxicity through the release of high concentrations of $Ca^{2+}$ and glutamate. Furthermore, NO alters the electron transport chain in the mitochondria, generating further FR by affecting enzymes with a sulfuric catalytic center, such as ubiquinone succinate [34]. In addition, iNOS expression and production of NO have a retroactive effect on the development of the inflammatory response, due to their role in the production of cyclooxygenase 2 (COX)-2, which increases the levels of inflammatory products such as prostaglandins and thromboxane [34, 35].

### *2.1.7. Inflammatory response*

Immediately after the traumatic rupture of the BBB, an inflammatory reaction takes place. This reaction involves the actions of chemical mediators and the participation of inflammatory cells, derived from the activation of resident immunological cells (astrocytes and microglia) and recruitment of peripheral cells (macrophages, lymphocytes, etc.) [8, 36].

The production and release of pro-inflammatory cytokines and chemokines are some of the first inflammatory events triggered after SCI. Cytokines such as IL1, IL6, and tumor necrosis factor-alpha (TNF$\alpha$) are known as mediators of the peripheral inflammatory response, and are

synthesized and released by various cells in the CNS. TNF$\alpha$ promotes the immediate recruitment of neutrophils to the damaged site by inducing the expression of molecules, such as endothelial cell intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1). It also stimulates the release of IL8, an important neutrophil chemotactic factor, which modifies endothelial cells permeability and consequently affects the BBB. Furthermore, TNF$\alpha$ also stimulates astrocyte proliferation and hypertrophy, promoting the formation of a glial scar that acts as a barrier against possible regeneration [37, 38].

During the inflammatory response, the infiltration of immunological cells is the principal contributor to neuronal degeneration. These cells are guided from the periphery to the injury site by chemokines and cytokines released by microglia cells and astrocytes, which conjointly with peripheral macrophages constitute the main components of the injury [10, 39]. These events begin with the acute inflammatory response and persist in the chronic phase, characterized by a constant migration of cells (neutrophils, macrophages, lymphocytes, basophils, and eosinophils) from the periphery. This leads to the increased levels of inflammatory cytokines and extended damage, as well as the increase in neural destruction, which hinder the possibility of reparation and tissue regeneration [40, 41].

After injury, two infiltration waves have been described. The first wave, constituted by polymorphonuclear cells (PMN), predominates during the first few hours following injury. Neutrophils appear in the vein and venule walls surrounding the injury within the first 4 hours and have been observed from 8 to 24 hours post-trauma. The inflammatory response is reflected by increased number of leukocytes in the cerebrospinal fluid (CSF), infiltration by PMN, an increase in leukotriene levels (mainly $LTB_4$), and myeloperoxidase activity [41]. The second infiltration is characterized by the presence of macrophages, which are observed in the first 2 days, reaching peak levels at day 5–7. After 2 days, proliferation and recruitment of macrophages and microglia occurs, alongside leukocyte infiltration from the third to seventh day. All of these alterations and phenomena that occur in a molecular environment promote gradual tissue degeneration, destroying the necessary anatomic substrate for neurological recovery [40].

Macrophage and monocyte infiltration after SCI aims to remove cellular debris and stimulate the infiltration of new blood vessels and parenchymal cells. The infiltration of these cells helps T-cell interaction, regulating their activation and proliferation through their role as antigen-presenting cells (APC) [42]. The microglia are pluripotent resident cells capable of expressing different phenotypes. The intensity of inflammatory response varies according to lesion severity, affecting cell recruitment and the magnitude of the immune response at the site of injury. Regulation of the inflammatory response occurs due to the interaction of the microglia with T cells, leading to their activation against specific antigens, and thus regulating the immunological response and subsequent phases [43].

Microglia cells are distributed across the CNS, serving as pathological sensors, which react to harmful stimuli [44]. The activated microglia migrate to the pathogen-invaded injury site and transform from the resting phenotype (ramified cells) into amoeboid cells (phagocytic) [45]. Activated microglia can release a series of cytokines, chemokines, and enzymes, depending on the activation stimulus, including: IL1-$\beta$, IL-6, TNF$\alpha$, transformation growth factor-$\beta$1 (TGF-$\beta$1), macrophage-colony stimulating factors (M-CSF) [46]; iNOS, neural growth factor (NGF), neurotrophin-3 (NT-3) and brain neuronal derived factor (BNDF) [43, 47].

Lymphocytes are cells that modulate the intensity of the inflammatory response. Their participation following SCI has also been related to neural tissue damage due to their production of pro-inflammatory cytokines, such as IFNγ and IL1β [43, 48]. IFNγ is directly related to neuronal destruction, inducing the expression of further pro-inflammatory cytokines (TNFα, IL6, IL12, and IL1β) and pro-inflammatory molecules (ROS and iNOs) through induction of nuclear factor kappa B (NFkB) and activator protein-1 (AP-1) signaling pathways [11, 43, 49].

After SCI, a self-reactive/autoreactive response, defined as an immune response against autologous constituents, is triggered within the CNS [50–52]. This response targets neural constituents, such as myelin basic protein (MBP), promoting an increase in the expansion of neurological damage at the injury site. This response is capable of increasing the damage to the nerve tissue, but is also able to promote protection and even restoration of damaged tissue [48, 52–55].

### 2.2. Chronic phase

In chronic stages of SCI, the formation of a barrier occurs, precluding axonal regeneration in the area surrounding the lesion. This barrier consists of two main components: glial (astrocytes) and fibrotic elements that synthesize inhibitory molecules, hindering interconnection and axonal regeneration [56]. It has been observed that the cicatrization process restores the vital function of the blood–brain-barrier and limits the resulting damage at the injury site. However, in addition to having beneficial effects, this process also prevents restoration [57].

During this phase, some disturbances regarding the organization of fibers are observed, such as demyelination, Wallerian degeneration, oligodendrocyte apoptosis, and the formation of a scar of collagen fibers [56, 58, 59]. In this phase, a strong, nonregulated interaction between the CNS and the immune system takes place, which includes the vegetative innervations to the lymphatic and endocrine tissue that aggravate the degeneration process of major functions [57].

The glial scar around the injury is formed by a wide net of fibrous astrocytes and collagen fibers, which release proteoglycans and neurofilaments, such as vimentin and nestin, which act as inhibitory molecules of neural growth [59, 60]. Therefore, the fibrous scar developed after an injury in the CNS is considered a hindrance for axonal regeneration [59]. Although traditionally astrocytes have been considered to be detrimental to regeneration, they possess beneficial effects when presented in their reactive form at the glial scar, including BBB repair and modulation of the immune response [61].

Astrocytes present a gradual response to the lesion, including changes in gene expression, hypertrophy, extension of the process, and in some cases cellular division [62, 63]. The currently known factors responsible for increasing the formation of glial scars in SCI are transforming growth factor β (TGF-β) [64] and INF-γ, among others [62].

Reactive astrogliosis, defined as an atypical increase of astrocytes, is characteristic of astrocytes surrounding the lesion. This phenomenon presents with a rapid synthesis of intermediate filaments, such as glial fibrillary acidic protein (GFAP), vimentin and nestin. Moreover, there is an excessive secretion of extracellular matrix (ECM) components, such as tenascins, type IV collagen, and chondroitin sulphate proteoglycans (CSPGs), which form a glial scar at the injury site. This scar develops into a fibrous barrier, preventing regeneration of nervous

connections adjacent to the lesion. Furthermore, the reactive astrocytes contribute to the release of pro-inflammatory cytokines, such as TNF-$\alpha$, INF-$\gamma$, IL-1$\beta$, and IL-6, which inhibit differentiation processes of neural stem cells (NSC) [65], and contribute to the chronic inflammatory response [62].

In addition, the formation of a glial scar favors cavitation, a process detrimental to regeneration at the injury site. This phenomenon can lead to the extension of the injury size days or even weeks after the lesion, resulting in the formation of an encapsulated scar, which prevents neuronal connection [66, 67].

At the chronic stage, the central canal is frequently involved in fluid-filled cyst development, which gives rise to malformations in the SC parenchyma; this condition is known as syringomyelia [68]. This term, first introduced by Ollivier D'Angers in 1827, derives from the Greek word for tube (syrinx) and is used to describe dilation of the central canal extending over many segments. Before trauma, CSF normally flows into the inner parts of the brain and SC. However, SCI evokes morphological changes, which disrupt correct circulation enhancing the volumetric growth of cavities. Syringomyelia appears to be related to irregular pressure conditions and hydrodynamic mechanisms related to the CSF [68, 69].

Hydromyelia, a closely related term that is often used interchangeably, also refers to a dilatation of the central canal by CSF. Some have defined hydromyelia as a congenital dilatation [70] of the central canal, which is partially lined with ependymal cells, strongly associated with hydrocephalus, an obstruction of the foramina of Luschka and Magendie [71]. The term syringomyelia has been affixed to every kind of intramedullary cyst, with some authors defining it as a cavity distinct from the central canal and lined by ependymal cells or primarily glial cells [71, 72]. However, others restrict its use to certain subtypes of cystic lesions and distinguish syringomyelia, hydromyelia, or myelomalacia as separate entities. In spite of this, some authors combine these terms into syringohydromyelia or hydrosyringomyelia [71]. Lee et al. stated that a clear communication between intramedullary cavities and the ventricular system is rarely demonstrated, making it difficult to differentiate syringomyelia from hydromyelia, although a truly eccentric location within the spinal cord may be more characteristic of syringomyelia than of hydromyelia [73]. Batzdorf states that the distinction between syringomyelia and hydromyelia is no longer considered absolute or critical [72].

## 3. Therapy after acute SCI

In recent years, neuroprotective or neuroregenerative strategies regarding the injury site have been chosen to mitigate autodestructive events following a SCI. These strategies include: preservation or regeneration of damaged neural tissue, neutralization of toxic mediators, and increasing tissue resistance to toxicity [74].

Although there is a substantial evidence showing new preclinical strategies that aim to promote neuroprotection, achieved with certain efficiency in murine SCI models [75], there are few clinically approved treatments available to patients with SCI. Currently, clinical treatments

are limited to surgical decompression, blood pressure control, and the possible use of methylprednisolone (MP), which is not recommended due to its secondary effects [76].

However, for each treatment strategy, it is important to consider the time elapsed between the injury and the initial treatments, in order to promote a beneficial effect by inhibiting or diminishing secondary damage as rapidly as possible. Despite the promising results shown by several treatments, there is currently no therapy that satisfies all the requirements necessary for an optimal recovery [77].

### 3.1. Pharmacological therapies

During the last 25 years, different preclinical and clinical studies evaluating neuroprotection in SCI have been conducted. As previously mentioned, careful consideration of the time frame for treatment after SCI is essential when selecting a therapeutic option. At the clinical level, conventional norms have recommended initiating treatment within the first 3 hours following injury. However, some preclinical studies have begun treatment administration within the first hour after lesion, which complicates the clinical application of these therapies [75]. Diverse drugs have been used in preclinical and clinical studies, with each having different effects depending of the therapeutic objective. However, the majority of drugs studied as possible neuroprotective agents focus solely on one type of damage, with some being tailored to specific mechanisms of the primary injury. The vast majority of these have consisted of pharmacological treatments, although many preclinical studies have included additional therapeutic strategies for acute and chronic SCI. Current pharmacological agents used in the treatment of acute SCI can be grouped into: ionic channel blockers, inhibitors of N-Methyl-D-asparate acid (NMDA), and AMPA-kainate receptors, inhibitors of FR and LP, antiapoptotics, and immunosupressors or immunomodulators [77]. All the therapies and their therapeutic objectives are mentioned in **Table 1**.

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| Preclinical therapies | | | |
| Ionic channel blockers | | | |
| **Sodium** | | | |
| a) Tetrodotoxin | (−) Sodium entry channels after SCI | Binds to voltage-dependent sodium channels in nervous system cell membranes, facilitating motor function recovery by reducing long-term white matter loss, thus improving neural tissue preservation. | [78, 79] |
| b) Riluzole | | Increases the survival and reinnervating capacity of injured motor neurons; conferred significant neuroprotection and behavioral recovery, sparing both gray and white matter. | [80, 81] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **Calcium** | | | |
| a) Nimodipine | ↓Oxidative damage caused by FR | Decreases LP end products, such as MDA and 4-Hydroxy Acrolein, resulting in a better motor recovery. However, it should be noted that nimodipine does not allow membrane repair. | [82, 83] |
| **Inhibitors of NMDA and AMPA-kainate receptors** | | | |
| a) Memantine | ↓ Neurological damage by glutamate and NMDA. | Noncompetitive NMDA antagonist that prevents neurotoxicity. In combination with antiapoptotic agents, provides better histological and clinical results, diminished necrosis and apoptosis. | [84, 85] |
| b) Gacyclidine | (−)noncompetitive NMDA receptor | Improved motor recovery, neural tissue preservation in a dose–dependent manner. In rats, gacyclidine exerts dose- and time-dependent neuroprotection. | [86, 87] |
| c) NBQX | AMPA-kainate receptor antagonist. | Improves mitochondrial function and reduces levels of ROS and lipid peroxidation products. | [88] |
| **Inhibitors of FR and LP** | | | |
| a) PUFAs | ↓FR formation, scavenging of ROS and RNS. | Prevents white matter damage, increases synaptic connections, neuronal survival, and improves motor recovery. Possesses antioxidant and anti-inflammatory effects. | [89–96] |
| b) Glutathione (GSH) | (−) FR by the free thiol group. | Anti-excitotoxic peptide through the inhibition of the union between specific ligands and inotropic GluRs by the modulation of redox reactions. Improves motor recovery, rubrospinal tract neuronal survival, blood flow stabilization. | [97–100] |
| **Antiapoptotics** | | | |
| a) zDEVD-fmk | (−) Caspase 3 and 9 respectively | The application of z-DEVD-fmk reduces secondary tissue injury and helps preserve motor function. | [101, 102] |
| b) LEHD-fmk | | Electron microscopy showed that z-LEHD-fmk treatment protects neurons, glia, myelin, axons, and intracellular organelles. | |
| **Immunosuppressive or immunomodulatory drugs** | | | |
| **1. Inhibitors of cyclooxygenase** | | | |
| a) Indomethacin | (−) COX 1 and COX 2 | Mixed results: some report improved neurological function and blood flow to injury site, as well as decreased neuronal damage, while others report delayed recovery. | [103, 104] |
| b) Celecoxib | (−) COX 2 | Reduction of prostanoids and FR synthesis, inhibition of arachidonic acid pathways. Increased motor recovery and diminished damaged spinal tissue. | [103] |
| c) Meloxicam | (−) COX 2 | Improved neurological function, amelioration of LP. | [105] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **2. Immunophilin ligands** | | | |
| a) Cyclosporine A | (−) Calcineurin activity | Inhibits the proliferation of T-helper lymphocytes and interferes with cytokine production (IL-1, IL-2 e IL-6), cytoskeleton motility of neutrophils, and activation of iNOS or ROS production. Reduces LP levels, glutamate excitotoxicity, and demyelination processes, increasing neuronal survival and motor recovery. | [104, 106–109] |
| b) Tacrolimus | | NF-kB and caspase 3 inhibition, leading to improved recovery and reduced neuronal loss. In mesenchymal stem cells (MSCs) transplantation, improves MSCs survival and neurological recovery after SCI. Tacrolimus may induce neuroregeneration by binding to heat shock protein 90. | [110–114] |
| **3. Immunomodulatory peptides** | | | |
| a) Monocyte locomotion inhibitory factor (MLIF) | ↓ VCAM-1, pro-inflammatory cytokines (IL-1$\beta$, IL-6, IL-12, and IFN-$\gamma$) | Motor recovery and survival of ventral and corticospinal tract neurons associated with a reduction in iNOS gene expression and up regulation of IL-10 and TGF-$\beta$ expression. MLIF also reduces the concentration of nitric oxide and the levels of lipid peroxidation in systemic circulation. | [115, 116] |
| b) Nogo-A | (+) T-cell-mediated protective autoimmunity | Nogo-A-derived peptide p472 and the transfer of anti-Nogo-A T-cells showed a significant reduction in neuronal loss. Promotes motor recovery and the long-term production of BDNF and NT-3. | [117, 118] |
| c) A91 | (+)T-cell-mediated protective autoimmunity | Reduces LP levels, iNOS expression, NO levels, caspase 3 activity, and TNF-$\alpha$ concentration. A91 combined with GME induced a better motor recovery, a higher number of myelinated axons, and better rubrospinal neuron survival than A91 alone. | [100, 119–125] |
| **Clinical therapies** | | | |
| Methylprednisolone | (−) Immune response | Contradicting data, with some showing improved motor recovery and others showing no recovery and increased side effects. | [126–128] |
| Minocycline | Multiple anti-inflammatory pathways | Improved motor recovery and decreased cell death through inhibition of caspase 3, matrix metalloproteinases, NO levels, and TNF-$\alpha$. | [129–131] |
| GM-1 Ganglioside | ↓ Excitatory neurotoxicity | Improved motor recovery evaluated by American Spinal Injury Association (ASIA) motor, light touch, and pinprick scores. | [132–134] |

**Table 1.** Pharmacological treatments used in acute SCI.

### 3.2. Nonpharmacological therapies

Nonpharmacological interventions are frequently advocated, although the benefit and harm profiles of these treatments are not well established. This may be due in part because of methodological weaknesses in available studies. However, preclinical studies have demonstrated neuroprotective effect, although results from clinical studies remain controversial and require further studies. These treatments are summarized in **Table 2**.

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **Preclinical therapies** | | | |
| **Vitamins** | | | |
| a) Vitamin B3 (niacin) | Phenotypic shift in macrophages from M1 to M2 | Reduced p65 NF-κB phosphorylation, reducing M1 markers such as iCD86, IL-12, and IL-6 and increasing anti-inflammatory M2 markers, such as CD206, IL-10, and IL-13. | [135] |
| b) Vitamin C (ascorbic acid) | (−) FR formation | Reduces tissue damage and improves functional recovery in rats. | [136, 137] |
| c) Vitamin E (alpha-tocopherol) | (−) FR formation | Improves cell survival and motor function significantly following SCI. | [137, 138] |
| **Resveratrol** | ↑ Transcription factor Nrf-2 and sirtuin (SIRT) 1 | Reduces neutrophil infiltration, production of inflammatory cytokines (IL-1β, IL-10, TNF-α), and myeloperoxidase (MPO) by inhibition of NF-κB; diminishes iNOS expression, apoptosis, and caspase-3, as well as inducing important locomotor recovery. | [139–142] |
| **Gene therapy Chondroitinase gene therapy via lentiviral vector (LV-ChABC)** | (−) Chondroitin sulfate proteoglycans (CSPGs) | Reduced cavitation and enhanced preservation of spinal neurons and axons. Improved sensorimotor function and increased neuronal survival correlated with reduced apoptosis. | [143] |
| **Hypothermia** | Vasoconstriction,<br>(−) Inflammatory response | Decreases the degree of the hemorrhage at the injured site and neurotoxicity by reducing the levels of glutamate and glutamanergic receptors.<br>Prevents changes in the BBB, thus hindering extravasation of leukocytes into the CNS.<br>Inactivation of production of pro-inflammatory cytokines, such as IL-1β, IL-18, and TNF-α. Also reduces $O_2^-$, NO, and OH FR. Reduces cell death and apoptotic mechanisms through caspase-3 and cytochrome C inhibition. | [144, 145] |
| **Cell therapy** | | | |
| a) Schwann cells | (+) Myelination | Treatment with these cells improves sensitive and motor functions due to the | [146, 147] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| | | remyelinating potential of Schwann cells, permitting the transmission of action potentials through regenerated axons wrapped in Schwann cells. | |
| b) Embryonic stem cells. | Pluripotent cells capable of differentiating into every type of cell | Induce motor recovery through the ability to transform into astrocytes, oligodendrocytes, and/or neurons *in vitro* prior to transplantation, in order to avoid their tumorigenicity. | [148] |
| c) Olfactory ensheathing cells (OECs) | Found in the center and periphery of the olfactory nerve; capable of differentiating into neuronal or glial lineage cells | Enhanced locomotor recovery, axon myelination, and neuroprotection. | [149] |
| d) MSCs | Obtained from bone marrow; capable of differentiating into every type of cell | MSCs may facilitate recovery from SCI by remyelinating spared white matter tracts and/or enhancing axonal growth with low immunogenicity. Modulate the inflammatory microenvironment to reduce pro-inflammatory cytokine levels. | [150, 151] |
| **Low-energy extracorporeal shockwave therapy (ESWT)** | ↑ Electric stimulus | Improved motor and sensory recovery, decreased neural cell death. Stimulates angiogenesis and neurogenesis. | [152] |
| **Physical therapy** | ↓ Spasticity<br>↑Neurological outcome | Upregulates the expression of NT3, NT4, BDNF, and GDNF, while reducing levels of apoptosis-related proteins such as caspase 3 and 9.<br>Induces axonal regeneration, broadening the scope of physical therapy from neuroprotection to neuroregeneration. | [152–156] |
| **Clinical therapies** | | | |
| **Cell therapy** | | | |
| Autologous transplant of MSC | Obtained from bone marrow; capable of differentiating into every type of cell | Improved motor, sensory recovery, and neurological outcome.<br>Improved sexual function and bladder and bowel control<br>Increased levels of BDNF, NGF, NT3, and NT4. | [157–161] |
| Physical therapy | ↓ Spasticity<br>↑Neurological outcome | Further translational studies are required in order to provide favorable results in patients similar to those seen in animal models of SCI. However, patients with incomplete SCI saw an improvement on their ASIA score after receiving physical therapy. | [162–164] |

**Table 2.** Nonpharmacological therapies used in acute SCI.

## 4. Therapies for chronic SCI

Many patients with chronic SCI experience little partial recovery with the use of acute phase treatments. When compared to acute SCI treatments, the efficacy of therapies that promote axonal regeneration in chronic models is reduced due to the generalized stability, induced by protective means or restoration promoters not present during the acute phase [165]. Studies indicate that this period of stability is reached in up to 3 months [166], followed by a progressive decline of neurologic functions in rodents that underwent SCI [167, 168].

Treatments for chronic SCI focus on avoiding or improving characteristic pathophysiological mechanisms, such as glial scar formation, demyelination, and astrogliosis. Moreover, it must be emphasized that while strategies for acute SCI are limited to preventing further damage, therapeutic strategies for chronic SCI instead focus on promoting neuronal regeneration and treating accompanying symptoms of chronic complications. Pharmacological and nonpharmacological therapies utilized in the treatment of chronic SCI are summarized in **Tables 3** and **4**.

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| **Preclinical therapies** | | | |
| **Antagonists of Rho signaling pathway** | | | |
| a) C3 transferase | (−)Rho protein | Stimulates axonal growth and improves motor function. | [165] |
| b) Y27632 | (−)Rho protein, nonselective inhibitor | Promotes axonal regeneration and motor function recovery. | [166] |
| c) Fasudil | (−)Rho protein | Conjoint administration with MP promotes recovery of motor activity and reflex movements, as well as tissue preservation. | [167] |
| d) P21 | (−)Rho protein | Capable of stimulating axonal regeneration and improving motor function of extremities. | [168] |
| e) Ibuprofen | | Enhances recovery by limiting tissue loss and stimulating axonal growth. | [169] |
| **Glial scar inhibitors** | | | |
| a) 2,2′-bipiridine (BPY). | (−) prolyl 4-hydroxylase | Growth of corticospinal tract neurons through the injury site and improved motor function recovery. | [170] |
| b) Decorine | (−) TGF-β | Suppresses glial scar formation, favors axonal growth. | [171] |
| c) Olomoucine | (−) CDK1/Cycline B and related kinases | Limits astroglial proliferation and increases GAP-43 expression, improving motor function. | [172] |
| d) α,α′-dipyridyl | (−) prolyl-4 hydroxylase | Decreases collagen synthesis. | [173] |

| Therapy | Mechanism of neuroprotection<br>↑ Increase<br>↓ Decrease<br>(−) Blocked<br>(+) Activated | Treatment outcome | References |
|---|---|---|---|
| e) ChABC | (−) ECM molecules | Promotes spinal cord plasticity along injured corticospinal tract and uninjured serotonergic projections, facilitates growth of new fibers, and stimulates rubrospinal projection neuron growth. | [174, 175] |
| **Anti-Nogo therapies** | | | |
| a) Nogo receptor (NgR) | Myelin-associated inhibitors | NgR immunization markedly reduced the total lesion volume, improved locomotor recovery and grid walking performance. | [176] |
| **Clinical therapies** | | | |
| **Rho-ROCK inhibitor** Cethrin/VX-210 | (−)Rho protein | Significant improvement in long-term motor scores (18.5 ASIA points) for cervical patients. Currently under study in a phase III trial in patients with acute cervical SCI which commenced in 2016. | [177, 178] |
| **Anti-Nogo antibodies** | Myelin-associated inhibitors | Promotes axonal sprouting and functional recovery. | [117, 179] |

**Table 3.** Pharmacological therapies in chronic SCI.

| **Preclinical therapies** | | | |
|---|---|---|---|
| **Glial scar removal** | ↓ or (−) glial scar (Surgical) | Promotes axonal development, although surgical removal may lead to a second injury. | [180] |
| **Biocompatible matrices** | | | |
| a) Fibrin glue (Tissucol) | Fibrinogen and thrombin compound, potentially adequate biological vehicle for cell transplant. | Promotes growth and incorporation of primary myelinated and unmyelinated afferent axons, and intervenes in the support and directionality of axons with Schwann cells.<br>Fibrin-stabilizing factor (Factor XII), also contained in Tissucol, favors migration of MSCs on the highly reticulated structure of the glue and increases their proliferation. | [181, 182] |
| b) Alginate | Vehicle for drug release, cellular encapsulation and cellular transplant | Facilitates axonal guidance and cell adherence by delivering ECM components, such as fibronectin, laminin, collagen, and polyornithine, alongside progenitor neuronal cells. | [183] |
| c) Hyaluronic acid | Porous structures that gradually release growth factors, cellular encapsulation, or drugs | Minimizes the formation of glial scar and promotes astrocyte and microglia migration. | [184] |

| **Preclinical therapies** | | | |
|---|---|---|---|
| d) Polyethylene glycol | Seals injured membranes and allows them to reassemble | Repairs cell membranes in the CNS, although it does not provide three-dimensional support. | [185] |
| e) Matrigel | Matrix conformed by multiple growth factors and extracellular proteins | Compounds facilitate cellular adherence, differentiation, Schwann cell growth, and axonal regeneration. | [186] |
| **Cell therapies** | | | |
| a)Neural stem cells | Integrates with host circuits to enhance behavioral recovery | Improves phrenic motor output after high cervical SCI, improving spontaneous respiratory motor recovery. | [187, 188] |
| b) Mesenchymal stem cells | Modulate inflammatory response, promote angiogenesis | Promotes repair by anti-inflammatory molecule secretion and stimulation of macrophage polarization, secretion of trophic and neurotrophic factors. | [189–195] |
| c) Schwann cells | Stimulation of remyelination | Promotes angiogenesis, prevents apoptosis, and stabilizes the BSB through astrocyte regulation, forming axonal guidance filaments through the injury site. Increased preservation of white matter and host Schwann cells and astrocyte ingress, as well as axon ingrowth and myelination. | [196, 197, 201] |
| d) OECs | Phagocytosis of debris and microbes, growth factor signaling | Improves neurite outgrowth and endogenous remyelination, as well as white matter preservation, sensory, and motor recovery. | [198–200, 202–204] |
| **Combination therapy** | | | |
| a) Cocktail with 10 growth factors. | ↑ NT-3, BDNF, EGF, βfgf, GDNF, PDGF, αfgf, HGF, IGF-1, and calpain inhibitor in a fibrin gel conjointly with NSC transplantation | Induces significant motor recovery. | [205] |
| b) Anti-Nogo-A antibody followed by ChABC and physical rehabilitation. | Myelin-associated inhibitors<br>(−) ECM molecules<br>↓ spasticity | Spontaneous recovery of forelimb functions reflected the extent of the lesion on the ipsilateral side and improved motor recovery when compared to the groups receiving individual treatments. Histological results showed increased neuronal regeneration. | [206, 207] |
| c) ChABC and NSCs | (−) ECM molecules<br>Integrate with host circuits to enhance behavioral recovery | Allows the transplanted cells to differentiate into neuroglial cells and permits proper axonal regeneration and growth across the injury site, leading to significant motor recovery. | [208] |
| d) A91 and surgical glial scar removal. | ↑ Growth factor<br>(−) glial scar | Increases motor function.<br>Facilitates the axonal regeneration in the region caudal to the injury site. | [122] |

| | | | |
|---|---|---|---|
| **Preclinical therapies** | | | |
| e) Degenerated peripheral nerves with MSCs and fibrin glue | ↑ Growth factor<br>(+) neural regeneration | Induces axonal regeneration and myelination with molecules associated to GAP-43 and neuritin, which are present in axonal growth cones and axonal remyelinization. | [209] |
| **Clinical therapies** | | | |
| Physical therapy | ↓ Spasticity | Upregulation of BDNF, IGF-1, other growth factors.<br>Improves axonal plasticity and regeneration, motor function. | [210–215] |
| Muscle electrical stimulation | ↑ Muscle electric stimulus | Improvement in their motor and sensory function, as well as an increase in muscle size and strength | [216] |
| Spinal cord stimulation | ↑ Spinal cord electric stimulus | Treated patients were able to initiating limb movement and improve posture control, bladder emptying (urinary retention), and sexual function. This therapy also provoked escalated extension-flexion movements. Additional trials (NCT02592668, NCT02313194) are now ongoing to assess safety/feasibility and validate this exciting finding, with results expected by 2018. | [217] |
| Glial scar removal with NeuroRegen scaffold. | ↑ Spinal cord regeneration | Better recovery of autonomous nervous functions, as well as the recovery of somatosensory-evoked potentials of lower limbs. | [218] |
| **Cell therapies** | | | |
| a) NSC transplant | | Cervical transplant (n = 31; NCT02163876) and thoracic transplant (n = 12; NCT01321333). Preliminary results from these trials do not show increased complication rates, although results on motor and sensitive recovery remain pending. | [219, 220] |
| b) Oligodendrocyte precursor cells | | Asterias Biotherapeutics Inc. phase I/II dose-escalation trial (n = 35; NCT02302157).<br>This study is expected to be completed in 2018. | [220] |
| c) MSCs transplant | | Phase II/III clinical trial in South Korea (NCT01676441) by Pharmicell Co. with intraparenchymal and intrathecal administration of MSC. Results are still pending, with an estimated completion date of 2020. | [220–222] |
| d) Schwann cells transplant | | An open-label phase I trial (n = 10) by the Miami Project to Cure Paralysis is now | [220] |

| Preclinical therapies | | |
|---|---|---|
| | investigating Schwann cells in the treatment of patients with chronic ASIA A, B, and C cervical or thoracic injuries, with results expected by 2018. | |
| e) OECs transplant | Phase I clinical trial, with results showing an improvement in sensory and motor function, along with improved preservation of white matter at the site of injury. | [223, 224] |

**Table 4.** Nonpharmacological therapies in chronic SCI.

## 5. Conclusion

In conclusion, despite promising innovative advances in preclinical treatments, there is currently no consolidated therapeutic strategy at clinical settings. Further research is needed to establish novel therapeutic strategies, including immunomodulatory strategies and combinatorial therapy, in order to improve recovery and therefore the quality of life for patients.

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Chapter 3

# Spastic Paraplegias Due to Non-Traumatic Spinal Cord Disorders

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71457

**Abstract**

Spinal cord disorders are induced by diseases of various categories: infectious, inflammatory, degenerative, genetic, traumatic, and so on. These diseases involve spastic paraplegia or tetraplegia, abnormal sensation, bladder and anal dysfunction, etc. This chapter describes the medical etiologies and treatments for spastic paraplegias. I will mention diagnostic and therapeutic aspects of spastic paraplegias due to non-traumatic spinal cord disorders. I will describe my cases who suffered from amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), HTLV-1 associated myelopathy (HAM), and multiple sclerosis (MS). I also investigate the recent therapeutic strategies for spastic paraplegias. Spastic paraplegia is an intractable condition accompanied by many spinal cord disorders. Some therapeutic methods (intrathecal baclofen and botulinum toxin injection) have symptomatic effects. Rehabilitation and some devices are also effective for spasticity.

**Keywords:** adrenoleukodystrophy (ALD), amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), HTLV-1 associated myelopathy (HAM), multiple sclerosis (MS), intrathecal baclofen, botulinum toxin, rehabilitation

## 1. Introduction

Spinal cord disorders are induced by diseases of various categories: infections [1] (e.g. herpes zoster or human T-cell lymphotropic virus type 1), inflammation (e.g. multiple sclerosis [2]), vascular diseases (e.g. spinal cord infarction [3]), degeneration (e.g. amyotrophic lateral sclerosis [4]), genetic diseases (e.g. hereditary spastic paraplegias [5]), metabolic disorders [6], trauma, etc. These diseases involve spastic paraplegia or tetraplegia, abnormal sensation, bladder and anal dysfunction, etc. This chapter describes the medical etiologies and treatments for spastic paraplegias. Diagnostic and therapeutic aspects of spastic paraplegias due to non-traumatic

spinal cord disorders will be described. In this chapter, cases with X-linked adrenoleukodystrophy (X-ALD), amyotrophic lateral sclerosis (ALS), hereditary spastic paraplegia (HSP), HTLV-1-associated myelopathy (HAM), multiple sclerosis (MS) are introduced.

## 2. Adrenoleukodystrophy (X-ALD)

Adrenoleukodystrophy is an X-linked recessive disorder that affects the central nervous system white matter and the adrenal cortex [7, 8]. It is classified into several subtypes. The most frequent type is the childhood cerebral form, which initially resembles a behavior disorder and presents adrenal insufficiency, followed by mental impairment, cortical blindness, cortical deafness, spastic tetraplegia and convulsions. This form leads to a decerebrate state for a few years after onset. Whereas the adult forms are divided into adult cerebral, adrenomyeloneuropathy, and cerebellobrainstem. Here we present adult cerebral form case with cerebellar ataxia and spastic paraplegia.

A 53-year-old man was admitted to our hospital because of mental deterioration and gait disturbance. His uncle on his mother's side suffered from gait disturbance from 40 years of age. His total IQ according to Wechsler Adult Intelligence Score (WAIS)-III was 64. He showed emotional incontinence and attention deficit. Gingival pigmentation was noted. Neurological

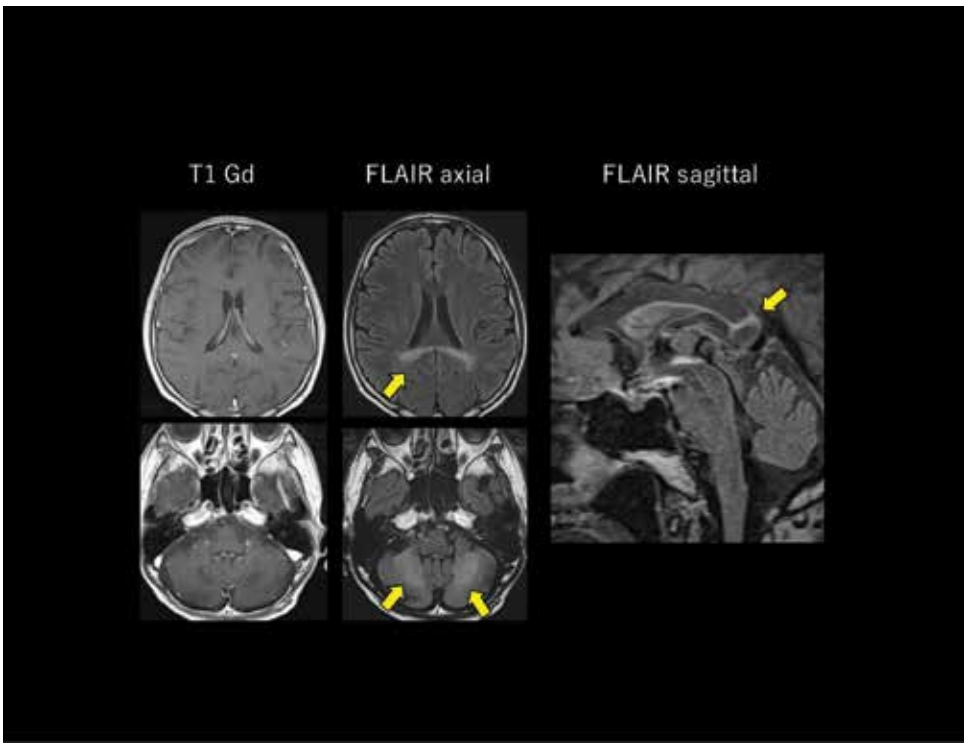


**Figure 1.** Brain MRI of the adrenoleukodystrophy patient. T1 gadolinium (Gd) enhance: no enhanced area in his brain. FLAIR axial: FLAIR hyperintensities in the cerebellar white matters and callosal body (arrow). FLAIR sagittal: FLAIR hyperintensities in the callosal body (arrow).

examination revealed saccadic eye movement, dysarthria, ataxia and spasticity of the bilateral feet, exaggerated deep tendon reflexes (DTRs), and bilateral positive Babinski signs. Blood examination disclosed elevation of very long chain fatty acids (C24:0/C22:0 2.09, C25:0/C22:0 0.080, and C26:0/C22:0 0.075) and ACTH (173 pg/ml). Brain MRI showed FLAIR hyperintensities in the cerebellar white matter and callosal body, whereas there was no gadolinium enhanced area (**Figure 1**). No atrophy or abnormal signals were observed on MRI of the spinal cord. Brain single photon emission computed tomography (SPECT) demonstrated cerebellar hypoperfusion. For an accurate diagnosis, gene analysis was performed by another institution, which revealed a non-synonymous missense variant of the *ABCD1* gene.

He was administered hydrocortisone and propiverine because of his adrenal insufficiency and frequent urination, and underwent physical rehabilitation (walking and balance exercise) for his leg spasticity and ataxia. We referred him to another hospital, and allogeneic hematopoietic stem cell transplantation was recommended [9, 10], but he denied this treatment.

## 3. Amyotrophic lateral sclerosis (ALS)

ALS is a fatal disorder characterized by muscle weakness and atrophy, and swallowing and respiratory disturbances [11]. The pathologic findings are upper (brain) and lower (spinal cord) motor neuron degenerations. In some ALS cases, spastic paraplegia can be a predominant symptom in the early stage of the disease. Here we present a case that showed spastic paraplegia as an initial phenotype.

A 60-year-old man was admitted to our hospital to alleviate his lower leg spasticity. Three years ago, he suffered from left leg discomfort and gait disturbance. Then the same sense of discomfort spread to his right foot. Neurological examination on admission showed marked leg spasticity with laterality and a spastic gait, exaggerated DTRs, and positive pathological reflexes. The brain and spinal cord MRI findings were normal. Motor evoked potentials suggested upper motor neuron disturbances.

We administered some muscle relaxants. He underwent gait rehabilitation and botulinum toxin injection to his lower legs. These therapies slightly improved the range of motion of knee and foot joints. But he refused intrathecal baclofen.

After 1 year, he noticed dysphagia and intrinsic hand muscle atrophy. Neurological reevaluation revealed bulbar signs and distal muscle weakness, these findings leading to a diagnosis of ALS. Although he underwent intermittent edaravone infusion therapy [12], his muscle weakness and atrophy gradually worsened and he became bedridden.

## 4. Hereditary spastic paraplegia (HSP)

HSP is a genetic neurodegenerative disorder that involves bilateral leg spasticity with additional features: mental impairment, peripheral neuropathy, cerebellar ataxia, retinal

degeneration, etc. [5]. Its progression is slower than that of ALS. We have encountered and described several cases who suffered from HSPs. First, I present a SPG3A case. SPG3A is an autosomal dominant, early-onset pure spastic paraplegia caused by an *Atlastin1* (*ATL1*) gene mutation [13].

A 52-year-old man visited our clinic because of early-onset gait disturbance at age two (**Figure 2**, IV-7). He had been diagnosed as having cerebral palsy by a doctor at another hospital. He underwent bilateral Achilles tendon lengthening in his early childhood. His older brother suffered from late-onset gait disturbance (**Figure 2**, IV-6).

On examination, his gait was spastic. Muscle weakness and atrophy of his lower extremities were observed. Exaggerated DTRs except for a diminished Achilles tendon reflex and pathological reflexes of his legs were noted (**Table 1**). MRI of his brain revealed no abnormal findings, whereas his spinal cord was slightly atrophic. Serum HTLV-1 antibody was positive, but he refused a lumbar puncture. Whole-exome sequencing analysis allowed the diagnosis of SPG3A. He had a reported heterozygous missense mutation (c.1239T>C, p.F413L) of the *ATL1* gene [14] (**Figure 3**).

This mutation was not detected in DNA from his father (III-1) or older brother (IV-6). We prescribed muscle relaxants (tizanidine and dantrolene), but he could not continue to take them due to their side effects (nausea and sleepiness).

Next, I present a SPG11 case. SPG11 is an autosomal recessive, complicated SPG accompanied by mental impairment, peripheral neuropathy and a thin corpus callosum. This disease is caused by mutations of the *SPG11* gene encoding spatacsin protein [15].

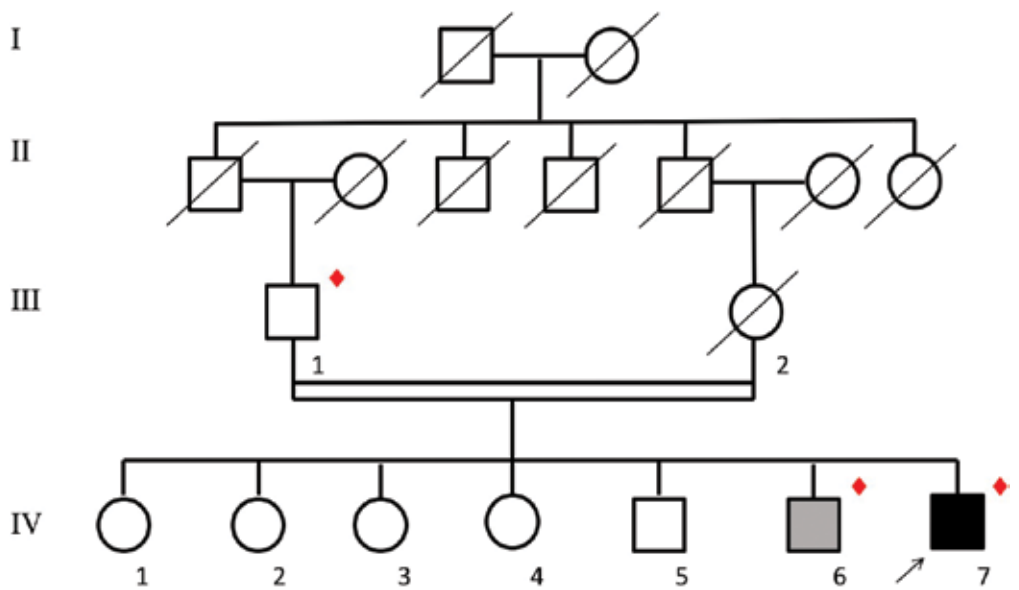


**Figure 2.** Family tree including the SPG3A/HAM cases. Proband (IV-7): SPG3A patient, HTLV-1 carrier. Older brother (IV-6): HAM patient. Father (III-1): Healthy HTLV-1 carrier. Diamonds indicate positive anti-HTLV-1 antibodies.

| | IV-6 (HAM) | IV-7 (SPG3A) |
|---|---|---|
| Age at examination | 54 | 52 |
| Age at onset | 42 | 2 |
| DTR of legs | ↑ | PTR↑, ATR↓ |
| Babinski reflex | + | + |
| Leg atrophy | − | + |
| Sensory disturbance | + | − |
| Spinal MRI | Normal | Mild atrophy |

**Table 1.** Clinical symptoms of the HAM and SPG3A cases.

A 31-year-old man was admitted to our hospital because of standing difficulty and bilateral leg pain. He noticed gait disturbance at age 13. His gait disturbance gradually worsened and he became wheel-chair bound at age 23. He has mental impairment. On examination, exaggerated DTRs and marked spasticity with sustained clonus of both legs were observed. Brain MRI showed a thin corpus callosum. Genetic analysis disclosed compound heterozygous mutations of the *SPG11* gene [16]. We tried intrathecal low-dose baclofen administration, which dramatically alleviated his spasticity (from 4 to 2, modified Ashworth score) and pain with leg clonus. Then an intrathecal baclofen infusion pump was implanted by a neurosurgeon. He became almost free from leg clonus pain with intrathecal baclofen and the modified Ashworth score decreased to 2 or 3.

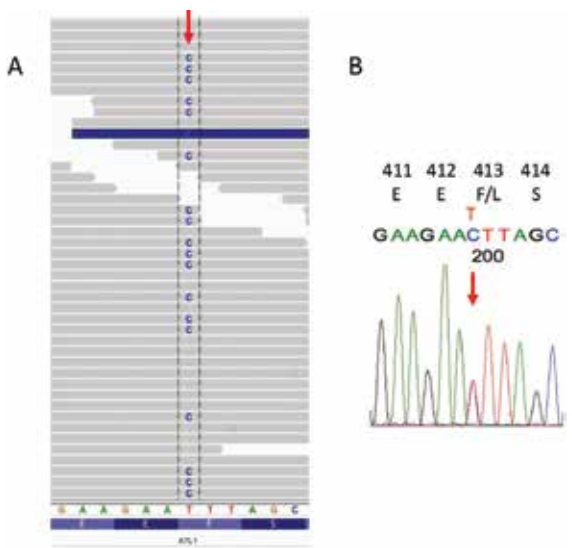


**Figure 3.** Gene analysis of the SPG3A patient. A. Whole-exome sequencing revealed the c.1239T>C (p.F413L) variant of the *Atlastin1* (*ATL1*) gene. B. Sanger sequencing confirmed the c.1239T>C (p.F413L) mutation of the *ATL1* gene.

## 5. Human T-lymphotropic virus type 1 (HTLV-1) associated myelopathy

HTLV-1 associated myelopathy (HAM) is a slowly progressive thoracic myelopathy characterized by spastic paraplegia with sensory and autonomic dysfunctions [17, 18]. There are many patients in the Kyushu district, the southwest part of Japan, because the prevalence rate of HTLV-1 carriers is high in Kyushu [18]. We found a HAM patient among the family members including a case of SPG3A (**Figure 2**, IV-6).

A 54-year-old man was admitted to our hospital for the further examination of gait disturbance. He first noticed the gait disturbance about 10 years ago. He walked without a heel and had urinary incontinence for 3 years. He pointed out increased deep tendon reflexes of his legs, a positive Babinski sign, and diminished deep sensation of the legs. On examination, increased leg spasticity was observed bilaterally (**Table 1**). Anti- HTLV-1 antibody was positive in both serum and cerebrospinal fluid (CSF). Serum from his healthy 91-year-old father (III-1, **Figure 2**) was also anti-HTLV-1 antibody positive, probably due to blood transfusion. Mild pleocytosis (8/mm$^3$), elevated neopterin (49 pmol/ml), and positive HTLV-1 proviral DNA were observed in his CSF. Whole-exome sequencing of his DNA did not identify pathogenic variants of the SPG3A and other SPG genes. We treated him with oral prednisolone [19], the symptoms did not worsen after that.

## 6. Multiple sclerosis (MS)

Multiple sclerosis (MS) is a neuroinflammatory disorder involving the spinal cord, optic nerve and brain, and is prevalent in young women. It takes relapse and remission courses. The characteristic finding is multiple lesions in the brain and spinal cord observed on MRI [20]. Neuromyelitis optica (NMO) is a similar disease to MS, but usually long cord lesions (>3 vertebral body) are observed on spinal MRI, and autoantibodies against aquaporin 4 are usually detected in patients' sera [21, 22].

A 47-year-old woman was admitted to our hospital because of gait disturbance, clumsiness and numbness of the bilateral hands. Neurological examination revealed leg spasticity, increased deep tendon reflexes of all extremities, extensor plantar responses and sensory disturbances of the bilateral upper extremities and trunk. Spinal MRI showed a central cord lesion at C2-C3 with mild enhancement (**Figure 4**). Multiple ovoid periventricular lesions were observed on brain MRI. However, clinically spasticity was presented in the clinical examination in the lower legs only. The anti-aquaporin 4 antibody was not detected in her serum. We started high-dose methylprednisolone pulse therapy and subsequently administered oral fingolimod for relapse prevention. Her symptoms gradually improved except for the leg spasticity. Then we tried to treat her with botulinum toxin injection to her legs and gait rehabilitation [2]. The modified Ashworth score for her legs improved from 3 to 2.

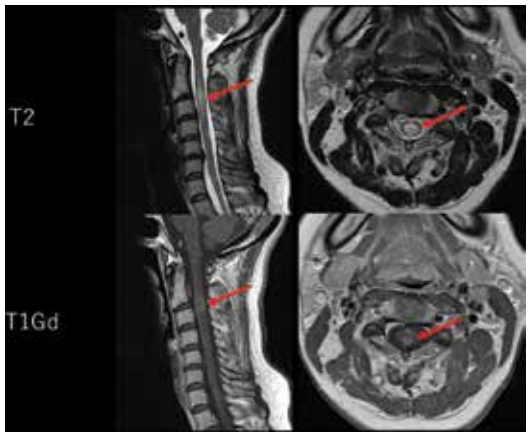


**Figure 4.** Spinal MRI of the multiple sclerosis patient. T2: T2 weighted image; central cord lesion in C2-C4 (arrow). T1 Gd: T1 weighted gadolinium enhancement; mild enhancement of C2-C3 lesion (arrow).

## Acknowledgements

We greatly appreciate the *ABCD1* gene analysis by Professor Nobuyuki Shimozawa (Division of Genomics Research, Life Science Research Center, Gifu University).

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Chapter 4

# Penetrating Spinal Cord Injury

Moti M. Kramer, Asaf Acker and Nissim Ohana

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.76857

**Abstract**

Penetrating spinal cord injury (SCI) is a relatively rare entity affecting mainly young males and military personnel worldwide. These injuries are the source of permanent disabilities to the affected patient and family and have substantial social and economic concerns. This chapter is an overview of the common penetrating spinal cord injuries, their incidence worldwide, causes, primary evaluation, and treatment including medical treatment and late definitive surgical treatment. It also describes common complications and strategies preventing secondary and collateral damage and disability.

**Keywords:** spinal cord injury, trauma, gunshot wound, paralysis, surgery, ATLS

## 1. Introduction

Spinal cord injury (SCI) and the lifelong disabilities associated with it are of a major concern to the society worldwide. Those injuries bear substantial personal and economic burden. Traumatic SCI is a subgroup of spinal cord injuries that affects mainly young males at their third decade of life, and its rate of incidence stays unchanged in the last three decades [1, 2]. Traumatic spinal cord injury can be divided into penetrating and blunt or non-penetrating injuries. Traumatic injuries have a steady incidence ranging from 12.1 to 57.8 cases per million annually [1, 2]. The most common etiologies are motor vehicle accident (MVA), falls from height, violence including gunshot injuries, and sport activities. Penetrating spinal injuries can be further divided into missile-penetrating spinal injury (gunshot, shrapnel, etc.) and non-missile-penetrating spinal injury (i.e., stabbing).

Penetrating gunshot injuries have been described as accounting for 17–21% of all spinal cord injuries [3]. Non-missile-penetrating spinal cord injuries are rare and account for less than 1.5%

of the total penetrating injuries [3]. The incidence of missile-penetrating SCI varies, and difference exists between its incidence in civilian population and military personnel population, where the latter is naturally more prevalent and influenced by eras of military conflicts [3].

## 2. Non-missile-penetrating spinal cord injury

Historically, the first non-missile-penetrating spinal cord injury (NMPSCI) was described by the Egyptians in 1700 BC. The Edwin-Smith papyrus was the first manual of military injuries in history and described different injuries and their proposed optimal treatment. Unlike other medical documents preserved from that era, the papyrus was based on medical procedures and not myths or prays [4]. In the second century AD, the Greek physician Galen reported his experiments on monkeys when a horizontal cut through their spine resulted in loss of sensation and motion below the level of the injury [5].

The largest series of NMPSCI was published by Lipschitz [6] with two case series in 1955–1967. Other smaller series were described in 1977 and 1995 [7, 8]. These publications came all from the same country (South Africa), both at an era of severe violence that unfortunately flooded the country.

Unlike in the rest of the world, in South Africa penetrating SCI is still responsible to about 60% of all SCI (spread evenly between NMPSCI and MPSCI). MVA, which is the most common cause of SCI in the rest of the world, accounts only for one-third of the cases in South Africa today [2].

Most of the affected victims of these injuries are young men in their second and third decades [2, 3]. Generally speaking, while in the past, NMPSI was rare in females, today the trend is changing, and over the past decades, it is seen more, especially in North America. Yet, about 80% of the affected victims of these injuries are males [2].

Knife is by far the most common assault weapon causing NMPSI. It accounts for 84% of the cases [9]. Other sharp objects such as screwdrivers, scissors, garden forks, and bicycle spokes were reported as the assaulting weapon for NMPSCI as well [9]. Even a pencil was reported as a stabbing object that caused NMPSCI [10].

Previous reports described a series of NMPSCI caused by acupuncture needles [11]. The World Health Organization published a systematic review of acupuncture-related adverse events in 2010, in which 44 cases of dural and arachnoid bleeding, causing severe adverse events and death (three cases), were reported [11].

Most non-missile-penetrating injuries happened when victims were stabbed from behind with the thoracic spine being the most common site (up to 63%), followed with cervical spine (up to 30%) [12]. A recent study examined that there are no differences in stab wounds to the neck, between military personnel (during combat) and civilians. This probably emphasizes the role of incidence in this type of injuries [13].

Victims are usually stabbed once, and the attacker usually withdrawals the stabbing object from the victim's body. However, in some cases the stabbing object brakes inside the body,

http://dx.doi.org/10.5772/intechopen.76857

and retained material occurs (**Figure 1A** and **B**). In the case of knives, the most common brakeage occurs at the handle or blade wedging a bone. The first one is usually very prominent from the victim's body and raises the dilemma of removing it at the scene [14].

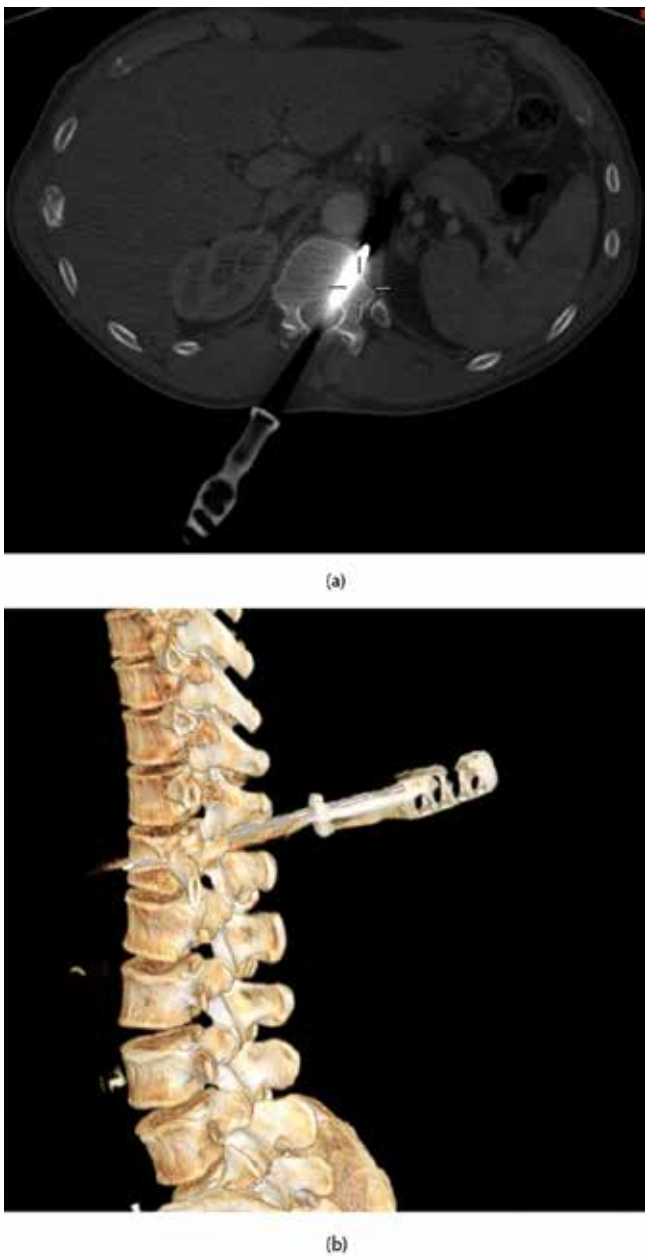


**Figure 1.** Axial CT scan (A) and 3D CT reconstruction (B) demonstrating a screwdriver going through the T12 vertebra, through the cord, and coming out adjacent to the aorta. The patient was fully alert on arrival with no neurological deficits. The screwdriver was removed in theater without complications, and the patient was discharged 2 days later.

The possible neurological deficit ranges from asymptomatic dural tears through different nerve root injuries, ranging from neurapraxia to neurothemesis and ending in the worst cases with complete or incomplete spinal cord injury.

The most common incomplete NMPSCI reported was the Brown-Sequard syndrome [15, 16]. This syndrome was first described by Charles-Édouard Brown-Séquard, in farmers cutting sugarcanes in Mauritius and sustaining hemisection of their spinal cord by long knives (1852) [17]. The syndrome is still the most common incomplete SCI [18].

Neurological injury to the spine may occur in two different mechanisms: immediate, through direct damage to neurological tissue, and delayed, following vascular injury to one of the feeding vessels in which a vessel that supplies the cord, most commonly the aorta or the Adamkiewicz perforant, is injured. The first one will cause most frequently an incomplete SCI, most commonly Brown-Sequard syndrome, while the last one is more likely to cause a complete SCI. The second pattern is the delayed onset which is caused most commonly from CSF leaks, edema, granuloma, scar formation, and infection. The delayed pattern can appear anytime from 2 years after the injury and up to 36 years as was described in a rare case of metal encrustation of a retained knife fragment in the spinal canal [19].

### 2.1. Primary evaluation: emergency department

All NMPSCI patients should be treated like other trauma victims according to the ATLS (Advanced Trauma Life Support) principles [20]. When the retained weapon is clearly prominent from the patient's body, the attention of the treating personnel tends to focus on it and distract them from acting according to the ATLS protocol. These injuries are sometimes less visible than it might be seen at first and may harbor other damages such as large vessels, heart, tracheal, or lung injuries that can affect hemodynamics, airway, and breathing and may be fatal. This is why any suspected patient should obtain an appropriate initial assessment and resuscitation before taking the next step. The initial assessment should not delay instance evacuation with minimal movements to the nearest hospital.

Extracting the penetrating object must not be done on site, not even at the emergency room, before obtaining proper imaging studies. These should include radiographs, sonography, and computerized tomography, according to the involved area. In case the patient is hemodynamically unstable and does not respond to initial resuscitation, an immediate transfer to the operating room with no further delay must take place.

NMPSCI always entails the risk of a retained foreign body material. It is well described in the literature [12, 21]. Patients presenting with delayed wound infections following stab wounds that were irrigated and primarily sutured without further evaluation were documented [22–24]. This is why many authors recommend routine imaging of any penetrating injury, even if only a skin or fascia discontinuity is observed, with no obvious damage.

### 2.2. Imaging

There are many imaging modalities that can be used to evaluate patients with NMPSCI. This includes plain radiographs, upper GI studies, ultrasound, computed tomography with or

without contrast, and MRI. It must be remembered that imaging cannot replace clinical evaluation, judgment, or resuscitation. Imaging should be considered only in a hemodynamically stable patient.

*2.2.1. Radiography*

Enicker and his colleagues [12] published a large series of stab wounds that accounted for one-third of all SCI in their center. Forty-nine percent of these patients had retained foreign bodies where a knife blade was the most common object. Knife blades are easily identified by plain radiographs; however, the availability of CT scan in most ER in the developed world has shoved aside its role in cervical trauma. It still has a role in the evaluation of thoracic injury mainly for the evaluation of the associated lung injury and not for the demonstration of the foreign body.

*2.2.2. Computed tomography*

Computerized tomography is the mainstay in diagnosis of penetrating SCI. It is a fast and reliable modality that can scan any part of the body. It has the ability to demonstrate the thoracic or cervical column with the surrounding organs that may be involved in the injury. The main disadvantage of CT scan is its poor ability to demonstrate direct damage or pathologic changes of the neural tissue.

*2.2.3. CTA*

Saito and colleagues in their review [21] recommend CTA as the gold standard of imaging for penetrating SCI. It has all the advantages of CT plus the benefit of demonstrating blood vessels including extravasation, pseudoaneurysm, dissection, occlusion, and arteriovenous fistula. Angiography is still considered as the "gold standard" vascular imaging examination; however, CTA is gradually taking its place as an alternative. CTA has been proven to be as good as angiography and yet less invasive and faster which makes it suitable for diagnosis in such cases [21].

*2.2.4. MRI*

MRI is not used routinely as a diagnostic tool in these injuries. The main concern is potential migration of retained metal fragments that can further damage neurologic or other surrounding tissues. Other drawbacks are time, unavailability, and study quality in the presence of metal artifacts. On the contrary to its place in the acute setting, MRI has a major role in studying complications following the initial treatment. Patients who present with deteriorating neurological deficit, prolonged fever, CSF leak, or post-LP syndrome are expected to be further evaluated with an MRI.

*2.2.5. Others*

Other imaging studies may be used when clinical suspicion for specific collateral organ damage is raised. This may include sonography, Doppler, endoscopy, and barium contrast imaging studies. Those studies are not routinely used, and the need depends on the site of injury

(thoracic vs. cervical), clinical examination, and the results of CTA. Sonography is a quick, noninvasive, and readily available tool; however, the technique is highly operator-dependent, and air from the injury, artifacts from retained metallic fragments, and hematoma can limit its interpretation.

### 2.3. Treatment

As mentioned above, initial treatment of these injuries should be treated as any other traumatic injury, by the ATLS guidelines. After securing airway breathing and circulation, the spine surgeon can address the NMPSCI. The management of regimen to date is still controversial, which is understandable given the low prevalence of these injuries. To date no guidelines exist as for the proper management plan, and the published series described are too small to dictate any clear conclusions.

Most authors agree that in cases of progressive neurological deficits, radiographic evidence of neural tissue compression, or persistent CSF leak, early intervention should be considered. In case of spinal canal penetration with no neurological deficit or CSF leak, surgery is not mandatory.

There is no clear evidence that removal of the retained foreign body will improve the neurological status. The literature describes conflicting reports where in some, foreign body removal improves neurological status and in others, neurological improvement was seen even with retained small fragments. Unfortunately, no RCT (randomized control trials) are available to guide us which option is better. Therefore, each case should be evaluated independently. One should judge the potential damage of extracting the penetrating object compared with the probability of late complications in case of leaving it in place.

In most cases, decompressive procedures, most commonly laminectomies, hemilaminectomies, and dural exploration, are the procedures of choice, mainly because the injury comes from the back. In other rarer cases, mainly in the cervical spine, anterior decompression is indicated.

Most NMPSCI are considered as stable spine injuries, and in an awake and alert patient without distracting injury, clearance of the spine can be done by clinical examination [11, 13, 14].

The surgical management of NMPSCI is a controversial topic [2, 6, 12, 14, 15]. This is more so in cases with a complete SCI but exist also in incomplete SCI.

The literature supports the fact that early surgical intervention for spinal cord injuries caused by low-velocity missile-penetrating injuries (bullets) does not improve the neurological status [1]. There is no clear-cut evidence regarding NMPSCI given the infrequency of these injuries. Case reports describe improvement of the neurological status following emergent or late surgical removal of the foreign body, in some cases even months after the injury [12, 19]. However, this improvement can occur without intervention as well, as reported by others [2] who recommended observation only, in most of their patients. Surgical intervention in NMPSCI may reduce late complications such as decreasing infection rate, cerebrospinal fluid fistula, and arachnoiditis. Delayed myelopathy has been described years following injury with a retained foreign body up to 36 years after the primary insult [12]. When there is rapid

progression of neurological deficit or in case of incomplete SCI with radiographic evidence of cord compression (i.e., expanding hematoma, bony fragments, or a retained foreign body), it is a consensus to proceed with immediate surgical intervention.

Positioning a patient with a retained knife handle protruding from his upper back is a challenge. Intubation in an alert patient must be done on a lateral decubitus position, to avoid further damage. Fiber optic-assisted intubation is preferable in difficult cases.

Essential part of surgery is canal decompression. Ideally, it should be done from an uninjured part of the dura mater to the next uninjured space, one level distal and one proximal to the injured loci.

Direct repair of the dura in the immediate setting is controversial, especially in the thoracic spine. This area of the spine is the narrowest along the spinal column. Moreover, blood supply to this segment has been described as the watershed area. Direct repair of the dura mater in this zone raises concern of cord compression secondary to neural tissue swelling. This is why it was proposed by some authors to apply collagen matrix on the defect instead of primary closure. Others are more concerned with the risk of infection and thus repeal any use of sealing material [25].

### 2.4. Perioperative care

Intravenous administration of steroids in penetrating SCI has no role, and, moreover, it may raise the risk of infection [26, 27].

Preventive antibiotic treatment in the perioperative period is controversial. The incidence of meningitis following NMPSCI is very low [2]. However, the incidence of soft tissue infection around the stab wound is high. There are no evidences as to what is the recommended antibiotic therapy for these injuries; thus, no protocol was published. In the Lipschitz study [6], only 4 out of 252 patients developed meningitis and 2 developed superficial abscess. The authors did not describe whether these patients were treated with antibiotics around the surgery. They mentioned that antibiotics were prescribed to these six patients, only after sepsis was diagnosed. Our policy is to treat these patients empirically, like with open fractures, with a wide range of antibiotic therapies. When canal penetration is evident, we include CSF-penetrating agents such as third-generation cephalosporin, for 3 days.

### 2.5. Complications

Complications can be related to the spine injury itself or to the surrounding organs.

Spine-associated complications are continuous CSF leak; infection (less than 1% will develop chronic abscess and osteomyelitis) and rarely meningitis; chronic epidural granulation (sometimes will present as progressive myelopathy); and there are reports of arachnoiditis and syringomyelia. Retained foreign body reaction may present as late-onset myelopathy due to foreign body migration. Metal particles such as copper or silver may cause a marked inflammatory reaction, while nickel and lead particles can be a source of an intermediate reaction. Oxidation of metallic fragments and rust deposit were also described [28].

Extra-spinal complications are head injuries (5% of patients have low GCS on admission, and, hence, it may mask the diagnosis of SCI), vascular injury (most commonly, the carotid artery, but there are cases of injury to the vertebral artery as well) [29, 30], brachial plexus injury (it may superimpose cord injury), trachea and esophagus injury (the hypotheses is that these patients are too sick to survive), and thoracic organ injuries such as hemothorax, pneumothorax, and hemopneumothorax with a self-resolving emphysema. Less common injuries involve the major vessels, pericardium, and even the heart. Chylothorax and tear of the diaphragm were rarely described.

## 3. Missile-penetrating spinal cord injury

Missile-penetrating spinal cord injury (MPSCI) can be a devastating event and may cause severe and long-term morbidity and mortality. As in other SCI, these injuries have a substantial economic and psychosocial burden to patient, their family, and society.

MPSCI was first described in 1762 by a surgeon named Andre Louis that removed a bullet from the lumbar spine of a patient, who later on regained motion in his lower extremities [9].

Many famous fatalities of MPSCI are known throughout the history. Among them was Lord H. Nelson who was shot by a French sniper in the Trafalgar battle. The injury was to his shoulder, and he was described as experiencing immediate paraplegia. He died shortly after. Other known cases were the American presidents, J.A. Garfield and A. Lincoln. As a general rule, these injuries have a high rate of mortality and hence discouraged any treatment for many centuries [31]. Only at the end of World War II, surgeons started to treat it aggressively. Pool had reported [32] 57% marked neurological improvement with laminectomy compared with only 4.5% spontaneous improvement with previously untreated patients. Later, studies that were published following the Korea and Vietnam wars had shown no benefit of laminectomies in cases of complete and incomplete SCI. They concluded that surgery should be considered only in grossly contaminated wounds and for patients with progressive neurological deterioration [33–35].

MPSCI can be divided by the kind of the penetrating missile, that is to say, bullet vs. shrapnel or any other foreign body that penetrates, by blast, the patient body. Another way to classify these injuries is by the muzzle velocity of the shouting firearm: high versus low. The third option would be to classify them by the amount of penetrating particles—a solitary missile penetration versus multiple, usually combined with a blast injury. Segregation can also be done for civilian versus military injuries.

### 3.1. Epidemiology

Military MPSCI epidemiology depends greatly on military conflicts around the world. Like any other military injury inflicted, it is more common in areas of worldwide conflicts and less common in peaceful areas.

Civilian MPSCI are easy to quantify. This is now the third most common cause of spinal injury in civilian population accounting for one-fifth of all spine injuries after MVA and fall from height [36, 37]. They also account for 13–17% of all causes of spinal trauma [10, 38–41].

In both civilian and military injuries of the vast majority, more than 80% of affected victims are men, with the highest incidence at their third decade [42–46]. The most common involved level is the thoracic spine (approximately 50%), and the least is the lumbar spine [3, 37, 47–49]. The incidence of thoracic spine injuries tends to reduce in more developed armies with better personal protective equipment [50].

### 3.2. Ballistics

The term "ballistics" refers to the scientific analysis of projectile motion and is divided to three main stages:

- Internal ballistics refers to the projectile's behavior within the barrel of the firearm.
- External ballistics deals with the projectile's path and motion while in the air.
- Terminal ballistics describes what happens upon the impact with the target.

Wound ballistics is considered a subgroup of terminal ballistics and is the main concern of medical personnel [43, 51, 52]. Wound (terminal) ballistics, together with the characteristics of the damaged tissue and its reaction to the penetrating missile, dictate the severity of the injury and treatment strategy [53, 54].

Although surgeons are naturally mostly concerned with the terminal ballistics, understanding of the entire bullet course is crucial, since it has a direct effect on its introduction into the body and the extent of tissue damage.

#### *3.2.1. Internal ballistics*

All bullets are fired through a barrel, which is usually a tube of variable length with internal spiral grooving. The bullet is accelerated down the barrel to reach its final exit velocity due to high pressure expanding gases from the combustion of its propellant [55, 56]. During its path within the barrel, the bullet acquires its spin as it is engaged by the spiral grooves of the barrel. This spin is essential for the appropriate orientation of the bullet during its flight [57].

Bullets are usually classified as "high" or "low" velocity, which corresponds to the type of firearm they were shot from—a rifle or a pistol, respectively [58]. Low velocity usually refers to subsonic speed of about 350 m/s, while high velocity can reach up to 600–900 m/s [57].

The bullet itself, and most importantly—its mass, also influences wound ballistics, since the mass and velocity both comprise the well-known formula of kinetic energy = $1/2\ mv^2$. Thus, a bullet fired from a handgun of 6.35 mm caliber, with a muzzle velocity of about 350 m/s and a mass of about 3.5 g, carries the energy of about 85 J. On the contrary, bullet fired from an assault rifle, such as the 7.62 mm caliber AK-47, with a mass of 8 g and muzzle velocity of about 800 m/sec, may reach the energy of about 2100 J—almost 25 times more than a handgun [59].

#### *3.2.2. External ballistics*

Once leaving the barrel, a bullet is subjected to several forces that might influence its energy-delivering capacity. First, it is affected by the escaping gases just as it is exiting the barrel

[60] that might destabilize it and thereafter to the drag forces as it traverses the air, which increases with rising velocity [51].

This combination of forces acting on the exiting bullet creates an overturning moment, which causes the bullet to diverge from its original line of trajectory. This divergence is called "yaw," and it is expressed by the angle between the bullet's axis and the velocity vector [36, 61]. Because of the bullet's spin, yawing results in complex spiral revolution of the tip about its center of mass. Eventually, if the distance the bullet travels is long enough, yawing becomes irreversible, and tumbling occurs—meaning the bullet advances base-forward [62, 63].

It is quite clear that as the distance between the firearm and the target is shortened, these are less so-called disturbances to the bullet's path, and hence it can deliver more energy upon the impact. Muzzle velocity decreases significantly after 45 m for most pistol bullets and after 100 m for rifle bullets [64]. Unfortunately, most civilian gunshot wounds (GSW) are inflicted from an average distance of only 10 m [65].

### *3.2.3. Terminal ballistics*

Terminal ballistics is directly influenced by the internal and external ballistics, which delivered the bullet to meet its target in a certain condition. As discussed above, the energy entailed within the bullet upon the impact is the main characteristic that will influence its effect within the body and will determine the extent of the injury [66].

The other aspect that determines the amount of injury transferred to the body is the resistance to penetration of the body and the characteristics of the body surface and tissue. The ability of the body surface to resist penetration is influenced in turn by two factors—the presented area of the bullet, which increases with rising yaw up to a maximal impact surface when the yaw angle reaches 90°, and the bullet deformation upon impact, which has to do with its internal metal composition and structure [67].

As the bullet penetrates the skin, the energy transfer between the bullet and the tissue begins. As a result of the high level of resistance and drag that meets the bullet with its entrance, a high-pressure crushing effect develops in front of the bullet's tip, sometimes called the "shock wave," and together with the mechanical damage that occurs, while the bullet cuts through the tissue—these create one level of tissue damage [58, 68]. In contrast to the high pressure that develops in front of the bullet, as the bullet keeps on advancing, a vacuum is created in the back of the bullet, which in turn causes the tissue to collapse back.

This change of pressures causes the "cavitation" effect, which basically refers to the tissue's reaction to the very rapid change of pressures—the tissue first expands and then collapses back, leaving a tract within the tissue which is slightly larger in diameter than the bullet. The magnitude of the cavitation is directly related to the rate of energy transfer into the tissue and to the degree of yaw—the bigger the yaw, the bigger the cavitation [69].

The outer appearance of the body after the impact is not always suggestive of the true damage that lies within. With low-velocity handguns, the bullet usually does not cause cavitation, and

the damage is usually due to the mechanical impact of the bullet. Sometimes, there is not even an exit wound and the bullet stays within the tissue. Alternatively, high-velocity rifles usually have an exit wound, and they leave behind them a distinct tract, usually very damaged and often contaminated because of the "suction" effect of the wound. One might find cloth fragments in a wound cavity [70].

### 3.3. Initial evaluation and management

As in any other trauma, MPSCI should be first treated according the ATLS principles [71]. This initial evaluation will reveal concomitant injuries. Rapid evacuation to a hospital is crucial. This is especially true for the military scenario, in which more than one injury is the rule. The Prehospital Trauma Life Support and the Military Trauma Life Support (PHTLS and the MTLS) emphasize the importance of rapid evacuation from the scene of injury. It recommends that only securing airway and breathing together with partial circulatory control (control external bleeding) are done at the scene, and, thus, instead of doing the whole "ABCDE" scheme, the team should perform stages A, B, and half C ("scoop and run").

After arrival to the hospital, these patients are initially evaluated in the trauma bay by a multidisciplinary team. Following initial resuscitations and stabilization, physical examination is undertaken. The sensitivity and specificity of this were shown to be high, in detecting spinal cord injury (100% and 87%, respectively) [72]. It should be emphasized that civilian and military scenarios are different. In the civilian, most injuries are inflicted by low-velocity weapons with a solitary injury and less comorbidity. The evacuation period is normally short, and most patients arrive conscious to the emergency room. Neurological examination in this setting is more feasible and accurate. The opposite is true for the military scenario where most injuries are of high-velocity nature, and usually there is more than one injury. Usually, since most of casualties have a longer period of evacuation, they are brought to the trauma bay intubated, and thus their neurologic assessment is limited. The clinician should rely mostly on the anamnestic report of the evacuation team that considering the circumstance might not always be accurate.

After securing airway, birthing, and circulation, and after an initial neurologic assessment was performed, the patient should be completely exposed to inspect the entire body. Documentation of the entry and exit wounds should be done. It should be kept in mind that in high-velocity weapons, more than one exit wound may be found. In a low-velocity weapon, no exit wound is usually the rule.

Treatment for associated injuries to other organs should be addressed.

Tetanus prophylaxis history should be inquired and treated accordingly. In cases of unknown immunization, tetanus immunoglobulin is required in addition to toxoid treatment.

Antibiotic treatment is usually given; however, no consensus for the type and duration of treatment exist. Evidence to support different antibiotic treatments in cases of organ perforation such as the larynx/esophagus in cervical injuries compared with abdominal viscera in thoracic injuries is low. There is, however, some evidence to support administration of a wide range of antibiotic treatments as prophylaxis [73]. Interestingly, a Cochrane review

concluded that evidence exists for antibiotic treatment only for the first 24 h after initial debridement [74].

Most of the evidence exists for low-velocity injuries. There is less evidence guiding treatment recommendation in high-velocity injuries. We normally recommend empirically regimen of 3 days of prophylactic antibiotic which is discontinued if no sign of infection is observed.

### 3.4. Imaging

The mainstay of imaging for MPSCI is the CT scan. In some cases a retained metal fragment can be found in chest and pelvic X-ray routinely done in the trauma bay; however, these can provide limited information regarding concomitant injuries and spatial orientation.

#### *3.4.1. CTA*

CTA is usually available, is relatively quickly obtained, and gives sufficient information on other visceral injuries as well as bleeding. The only disadvantage is its inability to demonstrate neurological tissue with high accuracy. It should be reemphasized that an unstable patient should not be referred to CT prior to resuscitation and hemodynamic stabilization. In case of failure to achieve hemodynamic stability, patient should be taken to OR without any further delay. We routinely use CTA in any penetrating trauma as part of our protocol given the advantage of demonstrating major vessel injury and extravasation.

#### *3.4.2. MRI*

MRI has the ability to demonstrate neurologic tissue including direct and secondary injury. However, this is a time-consuming modality and probably not suitable for initial assessment in these scenarios. Some concern exists regarding retained metal fragment migration and further neurologic damage when performing the MRI. Copper and lead are the most common materials for bullet manufacturing. These materials are non-ferromagnetic and should not affect MRI [75]. The literature shows that MRI (up to 1.5 T) is safe to use in case of retained bullets [76–79]. Nevertheless, we recommend that the decision should be done on a case-to-case basis, especially if the penetrating missile is not a bullet.

#### *3.4.3. Others*

As mentioned above, other imaging studies may be used when clinical suspicion for specific collateral organ damage is raised.

### 3.5. Definitive treatment

Management of acute missile-penetrating SCI is multidisciplinary. The treatment is guided by many factors, but first and above all, the patient's respiratory and hemodynamic stability are defined by the ATLS guidelines. A hemodynamically unstable patient, whose primary resuscitation has failed, should be transferred immediately to angiography or surgery suite

without further delay. In a stable patient, treatment should be guided by the presence of other factors such as neurological status, mechanical stability of the spine, CSF leak, risk for infection, and other systemic injuries.

### *3.5.1. Indication for surgery*

There are no clear clinical guidelines to direct the treatment pathway in MPSCI, and hence each case should be treated individually. Some issues, however, should be considered:

Wound care: in high-velocity GSW, an extensive wound debridement and lavage should be performed in the OR given the expected large infected cavity and "wound suction effect" inserting debris into the wound [8, 45, 80]. A low-velocity, civilian-inflicted GSW (gunshot wound) can be treated locally in the ER and observed.

Loss of neurologic function: progressive loss of neurologic function with radiographic evidence of neural tissue compression either by hematoma, bone fragment, or foreign body is an absolute indication for surgery [81–85]. There is no doubt that the initial neurological status will dictate the fate of the patient's neurological function [84]. There is only minor evidence that demonstrate neurological improvement following early (24–48 h) intervention. This is especially true if the insult occurs in the cauda equine area [82, 83, 86]. However, there is more evidence to show that there is no improvement following surgery, especially if the injury occurs between the levels of T1–T11 and definitely in complete injuries due to high-velocity GSW [49, 62]. In low-velocity civilian injuries, these types of injuries might have better prognosis, depending on what was the initial clinical presentation.

Despite the above details, some subgroups of patients may benefit from surgical intervention, even in the presence of a complete or nonprogressing injury. This includes complete injuries of the cervical spine where a potential recovery of an affected level is anticipated or when the injury raises a mechanical issue that might be solved with surgery (**Figure 2**). When intervention is considered, one should remember that it has been shown to result in about 20% of complications compared to 7% for nonsurgical treatment [87]. Clinical discretion should be used in all cases.

Foreign body removal: foreign body, e.g., bullet fragments, shrapnel, and intact bullets, is considered an absolute indication for removal in cases of incomplete SCI, definitely when it is progressive. When there is imaging evidence of cord compression, early intervention has been shown to be beneficial in many studies [47, 51, 88].

Removal of bullets in cases of complete and static SCI is not efficient and will not restore any neurological function [47, 62, 86].

Another possible indication for bullet removal from the spinal canal is the concern of fragment migration (**Figure 2**). This might happen early [89] or late [90, 91] in the course of injury, as shown in some sporadic cases. In both cases, neurologic deterioration had resolved following the surgery. That is why some surgeons suggest preventing this complication by surgically removing the foreign body, especially in cases with easy access and expectedly low complications.

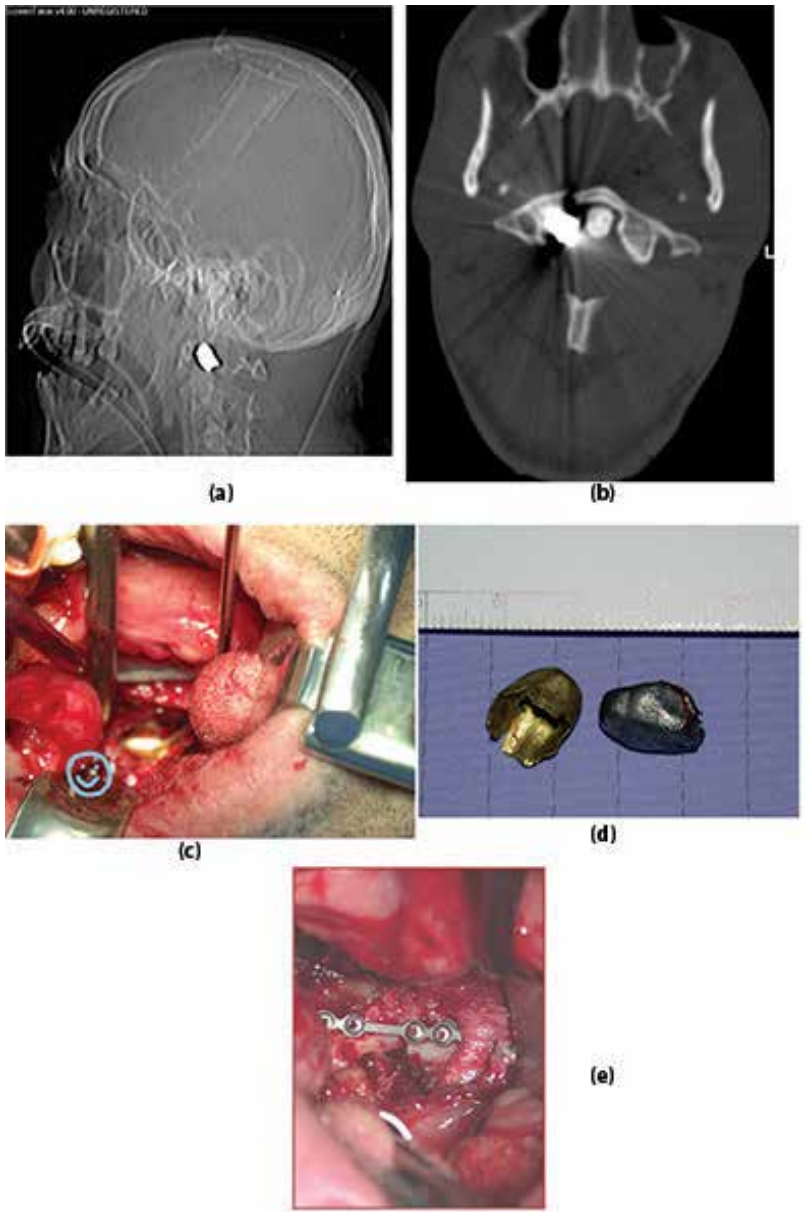


**Figure 2.** A 30-year-old patient, who sustained a low-velocity gunshot wound. He had a few entry wounds in his head and neck. He was conscious, alert, and hemodynamically stable with normal neurological status. The following images describe the evolution of events. (a) Plain radiograph showing the patient's skull with a bullet located at the center; (b) axial CT scan showing the broken arc of C1 with the bullet located next to the dens; (c) trans-oral approach to C1 vertebra with the bullet at the base of the surgical dissection. The smiley gives the orientation of the patient's face; (d) the bullet is shown outside of the patient's spine; (e) C1 ring following osteosynthesis.

The presence of foreign body inside the spinal canal was not shown to be associated with increased risk of infection, regardless of the previous path of the bullet, prior to its final location in the spinal canal [92, 93]. Thus, we do not consider bullet removal as an indication for

surgery in order to prevent potential infection. Metal toxicity is usually not a concern since most materials used to manufacture bullets and shotgun pellets today are often made of copper or lead.

Lead toxicity or plumbism was shown to happen in cases of retained bullets in joint spaces and intervertebral disks [94, 95]. The symptoms can include anemia, abdominal pain, anorexia, nephropathy, lethargy, encephalopathy, and motor neuropathy, all of which can appear intermittently or continuously. Symptoms develop insidiously and can appear even 40 years after the exposure [96], making the diagnosis often challenging. Missiles retained in bone and soft tissues are usually asymptomatic.

Spinal instability: low-velocity spinal GSW involving the vertebral column are normally stable and do not mandate surgical stabilization. Risk of instability is higher with high-velocity injuries. Preventive stabilization should be considered if instability is anticipated following the surgery. There are reports claiming that stabilization may improve neurology [44], and other reports state that it may facilitate rehabilitation [37].

CSF leak: should bullet or other foreign bodies enter the spinal canal, durotomy is suspected. If a clinical presentation of post-LP syndrome (positional headaches, diplopia, photophobia, nausea, and neck stiffness) presents, surgical exploration should be considered. The preferable treatment is direct repair of the dural defect. This might prevent fistula formation, secondary meningitis, cord herniation, and neurologic impairment. If primary repair is not feasible, like in the ventral cervical and thoracic cord, fibrin glue combined with synthetic or local graft should be used. Submuscular drains are controversial. Position restrictions (upright for cervical injuries or reclining for lumbar) are not mandatory and case specific. Subarachnoid continuous drainage is optional as primary treatment for minor tears or as an adjuvant to surgical repair.

The optimal timing of surgery for any indication is debatable [97–99]. Early surgical intervention has been reported to have less complication, while late intervention (more than 2 weeks) was associated with a high rate of arachnoiditis and spinal abscess [83].

No significant benefit of steroids has been shown [3]. A Cochrane review that shows some neurologic improvement in SCI following steroid administration (up to 8 h of injury) excluded penetrating injuries [100].

Empiric Intravenous antibiotic should be given for a minimum of 3 days and up to 2 weeks, in most cases. The covered spectrum should be wide in order to treat Gram-positive, Gram-negative, and anaerobic bacteria. This treatment was shown to prevent most infections including trans-colonic and trans-oral injuries [41, 81].

## 4. Summary

This chapter is an overview of two relatively rare-penetrating spinal cord injuries, their epidemiology, mechanism of injury, initial evaluation, and emergency primary and late definitive treatment. We also reviewed the complication and prognosis of each injury.

| | NMPSCI | MPSCI (high velocity) | MPSCI (low velocity) |
|---|---|---|---|
| Incidence | 1.5% of SCI | 17–21% of SCI | 17–21% of SCI |
| Primary evaluation | ATLS Extracting the penetrating object must not be done on site | MTLS "scoop and run" | ATLS |
| Preferred primary imaging | CTA/X-ray | CTA | X-ray |
| Surgical treatment | OR/observation<br>depending on neurological status and comorbidity | OR mandatory | ER/OR |
| Antibiotics | IV antibiotics (empiric) | IV antibiotics | PO antibiotics/observation |
| Steroids | No | No | No |
| Complication | CSF leak, infection(less than 1%), pneumo-/hemothorax, vascular (common) | Multiple organs-common. Spine instability, infection | Not common |
| Common incomplete SCI | Brown-Sequard syndrome | Any | Any, not common |

**Table 1.** Summarized table comparing evaluation, treatment, and complications between NMPSCI and MPSCI.

In order to emphasize the differences between these entities, we present a summarized table that compares between them (**Table 1**).

## Conflict of interest

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speaker bureaus; membership, employment, consultancies, stock ownership, or other equity interests; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this chapter.

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Chapter 5

# Infectious Complications after Spinal Cord Injury

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72783

**Abstract**

Infectious diseases after spinal cord injury (SCI) are important. They can cause mortality and morbidity. The SCI patients usually stay in hospital or rehabilitation units for a long time, and this can cause several complications for them.

**Infectious complications**: There are several infectious complications in these patients. Pressure ulcers that may be infected, soft tissue infections, osteomyelitis, pneumonia, urinary tract infection, bacteremia, meningitis, epidural abscess, and subdural empyema are important complications. These diseases should be diagnosed and managed promptly, before leading to irreversible complications or death.

**Diagnosis**: Diagnosis is made by physical examinations; laboratory tests like wound, urine, tracheal secretion, and blood culture with antibiogram; and radiologic evaluation like plain X-ray and magnetic resonance imaging may be used.

**Treatment:** Appropriate antibiotics are cornerstone of infectious complications. Offloading is important for treatment of pressure ulcers and subsequent complications such as soft tissue infection and osteomyelitis.

**Prevention:** Intermittent urinary catheterization and prophylactic antibiotic therapy can decrease UTI. Pressure relief, position changes, and regular and frequent observation of skin will prevent pressure ulcers, soft tissue infections, and osteomyelitis. Pulmonary toilet, appropriate positioning, and cough assistance can be useful for clearing retained secretions and preventing pneumonia.

**Keywords:** infectious, spinal cord, complications

## 1. Introduction

Infectious complications are supposed to be an important cause of morbidity and mortality in patients with spinal cord injury (SCI). Infectious diseases may lead to death and several

complications such as prolonged hospital stay and increased cost of management of patients. Several organs may be affected and problems in these organs can be even more important than the primary event. The types of infections in these patients are different and related to several factors. Inabilities to changing position or ineffective cough, using several necessary devices, prolonged hospitalization, and several other factors, in patients with SCI, predispose them to different types of infections. Inability to walk, sit, or change position may lead to pressure ulcers, skin and soft tissue infection, and osteomyelitis. Reduced tissue perfusion increases the spinal cord-injured patient's susceptibility to pressure ulcers [1] during the acute and rehabilitation phases, most frequently over bony prominences such as the sacrum, tuber ischii, heel, malleolus, and trochanter [2]. Physical and psychosocial elements such as nutrition, past history of pressure ulcers, and social supports can be important in developing ulcers [3]. Ineffective cough and retained pulmonary secretion may lead to pneumonia. Most of the patients need intubation in the course of hospitalization that predisposes them to ventilator-associated pneumonia. Ventilator-associated pneumonia is the most frequent nosocomial infection in patients receiving mechanical ventilation and contributes to a longer intensive care unit stay and high morbidity and mortality [4, 5]. Use of high doses of corticosteroid for management of some patients with SCI can increase the risk of infection. In those patients who need surgical intervention, the operation time is usually prolonged. Sometimes, the use of an external device is mandatory for fixation of unstable vertebral column. The SCI patients may develop bloodstream infection during the hospital admission. During bloodstream infection occurrence in an SCI population, multidrug-resistant organisms are frequent [6]. ICU-acquired bloodstream infection in the intensive care unit is still associated with a high mortality rate. The increase of antimicrobial drug resistance makes its treatment increasingly challenging. ICU bloodstream infection is associated with a 40% increase in the risk of 30-day mortality, particularly if the early antimicrobial therapy is not adequate [7]. Paying attention to antibiotic therapy is important in SCI patients. Antibiotic resistance is of great concern for both infection control and the treatment of infectious diseases. Drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter* and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, are associated with inappropriate antibiotic treatment that resulted in adverse outcomes. In addition, unnecessary use of broad-spectrum antibiotics for patients with non-drug-resistant pathogens increases mortality [8].

These can be the risk factors for developing infections in SCI patients. In this chapter, the cause of infections, predisposing factors, diagnosis, management, and prevention will be discussed.

## 2. Infectious diseases after spinal cord injury

### 2.1. Urinary tract infection

Urinary tract infections (UTI) still cause significant morbidity in patients with spinal cord injury, although mortality due to urinary tract complications has decreased dramatically [9]. Patients with spinal cord injuries (SCIs) and complete or incomplete paraplegia are prone to frequent, recurrent, or chronic UTI. The reason for the increased risk of acquiring UTI is

multifactorial, including reduced sensation of classical UTI symptoms, incomplete bladder emptying, frequent catheterizations, or chronic urinary tract catheters [10]. The rate of UTI in an SCI patient is 2.5 episodes in patient per year. UTI is the second leading cause of mortality in SCI patients [11]. Patients with SCI who have urinary catheters have an increased risk of UTI. Urinary tract infection can be important and can cause serious complications including sepsis and septic shock if it is not diagnosed and treated.

Using Foley catheter is usually accompanied with colonization of microorganisms and infection [12]. Bacterial biofilm formation of Foley catheter can cause cystitis [10]. About 80% of UTIs follow urinary catheter insertion. Nitrofurazone-coated and silver alloy-coated catheters can decrease asymptomatic bacteriuria during short-term (<30 days) use in comparison with latex or silicon catheters. The risk of infection is higher with long-term catheterization, and it is safe to remove it early after surgery. Latex and silicone catheters have the same infection rates, but Foley catheters cause more symptomatic bacteriuria and UTI than intermittent catheterizations. Changing the drainage bags and adding antiseptic solution to bags cannot prevent UTI in patients [13]. There are several risk factors for UTI in SCI patients. Reflux of vesicoureteral, postvoiding residuals, outlet obstruction, urinary tract stones, and bladder overdistension [14]. These patients are exposed to antibiotics because of frequent infections that may be an important risk factor for resistant microorganism infection [15]. Today, UTI may be difficult to treat in SCI patients because of antibiotic-resistant organisms. The SCI patients are also colonized by resistant organisms because of recurrent and prolonged hospitalization [16]. The main causative agent of UTI in SCI population is usually derived from the patient's flora. The indwelling catheter has a great role in infection and the duration of catheterization is the most important risk factor. If the patient carries a catheter more than 30 days, the risk of infection with multiple organisms will increase. Although short-term catheterization can be risk factor for bacteriuria, it is usually asymptomatic and often by a single microorganism [17]. It is better to use hydrophilic-coated catheter for intermittent catheterization in SCI patients during acute inpatient rehabilitation. These kinds of catheters can postpone the development of UTI. They also reduce the incidence of bacteriuria and infection. Reduction of complications and treatment costs and preventing the emergence of antibiotic-resistant organisms are other benefits of hydrophilic-coated catheters [18]. Substitution of indwelling catheter with intermittent catheterization during the rehabilitation phase will reduce development of UTI [9]. The unitary catheter should work in a closed system so that no organism can enter the system. It is also important to reduce the duration of catheterization. Sometimes intermittent catheterization, condom sheet catheter, and suprapubic catheters may substitute indwelling catheterization to reduce the risk of infection [17]. Intermittent catheterization is safe and is advised to prevent UTI in SCI patients. Condom sheet catheter can be used in patients who are able to urinate and there is no pathology or injury in urethra. In some patients, where using condom sheet catheter or intermittent catheterization is not suitable or possible, the physician may decide to use suprapubic catheter. The physicians should be aware of these two points that SCI patients may not have the classic symptoms of UTI and urinary infection may cause urologic complications [15].

### *2.1.1. Diagnosis*

Diagnosis of UTI is usually based on the results of urine culture, although in some condition like low titer of organism in urine, slow-growing pathogens and unusual organisms, results of culture may be unreliable [12]. The physician should be aware of how to diagnose UTI and distinguish it from colonization. These patients are at increased risk of acquiring multidrug-resistant bacteria because they are admitted due to UTI or other infectious diseases and take antibiotics. Several resistant organisms may cause UTI in SCI patients including multidrug-resistant *Pseudomonas aeruginosa*, ESBL (extended-spectrum β-lactamase-producing) *Escherichia coli*, resistant *Klebsiella* spp. and MRSA (methicillin-resistant *Staphylococcus aureus*) [10]. Due to multiple risk factors for acquisition of infection, especially with resistant organisms, complicated UTI may develop with unusual and resistant bacteria. The infection may be polymicrobial. Proteus, Providencia, Serratia, and enterococci may also cause UTI in these groups [9]. For the diagnosis of UTI, culture is needed to find to causative agent, but if the patient is not symptomatic, it is not necessary to get culture, because the patients usually do not need treatment [17]. When UTI is diagnosed in SCI patient, the physician should evaluate the patient for anatomical and functional disorders. It is important to correct any correctable disorder for optimal treatment success [9].

### *2.1.2. Treatment*

Differentiating infection from colonization and asymptomatic bacteriuria from symptomatic infection is an important point in treatment of UTI in SCI patient. A symptomatic patient needs to be treated, and after treatment, long duration of antibiotic suppressive therapy is not necessary [17]. For treatment of UTI, usually, there are many antibiotic options. It is better to postpone the treatment until the result of culture. Sometimes it is necessary to treat the patient empirically. Some variables like probable organism and susceptibility, administration route (oral vs. intravenous), the patient tolerance, renal function, and the patients' other medications should be considered for choosing appropriate antibiotic [19]. Duration of treatment of chronic UTI in SCI patient may need to be extended. Some studies recommend and some do not. It seems more studies are needed for certain recommendations [10]. The best antibiotics are those that have the most therapeutic effect on causative agent, without any or with less impact on the host normal flora. This antibiotic is best chosen according to result of urine culture and antibiogram. Duration of treatment is usually 5 days but may be extended to 7–14 days when reinfection or relapse occurs [9]. Some studies recommend treating urinary infection between 10 and 14 days in SCI patients, especially when it is not possible to discontinue the urinary catheter. To determine the optimal duration of treatment, multicentral and randomized clinical trial may be necessary [19]. Darouiche's study demonstrates that the 5-day treatment with urinary catheter exchange can be as effective as a 10-day regimen with catheter retention [20]. Antibiotics usually are chosen according to urine culture. Third generation of cephalosporines, carbapenems, and quinolones are often used to treat Gram-negative organisms. For treatment of *Enterococcus* and *Staphylococcus aureus* that usually are resistant in these patients (i.e., methicillin-resistant *S. aureus* or MRSA), vancomycin is appropriate.

*2.1.3. Prevention and prophylaxis*

Prevention of UTI in SCI patients plays an important role in hospital and even in rehabilitation courses of these patients. Paying attention to urinary tract hygiene is necessary. Some patients may encounter relapse or reinfection. In these patients, evaluation of structural and functional disorders should be performed. Duration of previous treatment and probable complications like urine residue and urinary stone should be assessed. Antibiotics may be used as prophylaxis, but it is important to notice that it can be used when recurrent UTI occurs and when all structural and functional abnormalities are corrected. Prophylaxis is not recommended for patients carrying indwelling catheters, and for those who have intermittent catheterization, it is contraventional [9]. Physicians can most effectively prevent UTI by avoiding use of long-term catheters, short duration of catheter use, and substituting intermittent catheterization with indwelling catheter. Daily washing of the catheter or perianal or periurethral areas has no preventive effect. It is recommended to use antibiotic immediately before any invasive procedure on urinary tract system [19]. Probiotics may be useful as prophylactic agents. They may decrease the number of resistant organisms' colonization and may be an attractive substitution for antibiotics for prophylaxis in future [16]. Non-antibiotic prophylaxis may be used for preventing UTI. Some studies may recommend cranberry juice as prophylaxis of UTI, but there is not any reliable clue to prove its effectiveness [9]. In Linsenmeyer's study, cranberry was used for prophylaxis of UTI in patients with neurogenic bladder after spinal cord injury. Cranberry tablets could not effectively decrease the risk of UTI in patients with neurogenic bladders [21].

## 2.2. Skin and soft tissue infection

One of the most important, serious, and chronic complications of spinal cord injury is pressure ulcer [22]. Pressure ulcers may cause long-term morbidity and even mortality and effectively have severe influence on SCI patients' lives [23]. These patients have more risk of developing pressure ulcer. The ulcers are often chronic wounds that debilitate the patient and increase hospital course [24]. Pressure ulcers are common in SCI patients and usually are complicated. Treatment is often difficult and expensive. It is important to pay special attention to pressure ulcer in SCI population [25]. Several risk factors are associated with pressure ulcer. These risk factors include: decreased activity, complete cord injury that cause paralysis, cervical collar and back board that cause restricted activity, diabetes mellitus, cigarette smoking, hypoalbuminemia, nursing home residence or long duration hospital stay [26], loss of sensation, wet area due to urinary or fecal incontinence, poor nutrition, and muscular atrophy. Pressure ulcers usually occur in about 30–40% of SCI patients. Ulcers usually develop on bony prominences. Sacrum, ischial tuberosity, trochanteric area and malleolus are usual areas for developing ulcers [2]. Patients with pressure ulcers may have good outcomes if rapid diagnosis and proper treatment is performed for them. The ulcer may heal completely without any sequelae. Some ulcers may have slow course of healing and some even may not heal. Some studies emphasize on the role of fibronectin on ulcer healing course. Fibronectin may have a role in opsonizing macro-aggregate debris for phagocytosis, increasing revascularization, and facilitating fibroblast proliferation and migration. Plasma fibronectin increases in ulcers

with rapid healing but stay in low level in ulcers with poor healing. So plasma fibronectin level may predict the speed of healing of pressure ulcers [27]. The SCI patients may also suffer from other soft tissue infection rather than pressure ulcers including fungal infections and seborrheic dermatitis [28].

### *2.2.1. Diagnosis*

Diagnosis of pressure ulcers is clinical. The ulcer smear and culture can be useful for recognizing the causative organism and determining the antibiotic sensitivity. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterococcus faecalis* are the most common organisms causing pressure ulcers [24].

### *2.2.2. Treatment*

Offloading is the cornerstone of treatment of pressure ulcers. Ultrasound (low-frequency and nonthermal) may have a therapeutic role in intact skin ulcers. If the ulcer is superficial, foam dressing and collagenase may be used. For deep pressure ulcers, usually debridement and surgical intervention is needed. Osteomyelitis beneath the ulcer is so important and should be considered in treatment of deep ulcers [23]. In SCI patients, flap surgery may be needed to cover the place of debridement [25]. In Schryvers's study on large number of SCI patients with pressure ulcers during 20 years, a large number of patients needed surgical intervention. Pelvic area ulcers were the most common (468 of 598 pressure ulcers), of which 431 (92%) were treated surgically. Fasciocutaneous or cutaneous flaps, muscle or musculocutaneous flaps and primary closures were the most common surgical intervention. During the ulcer management, some bone intervention is unavoidable [29]. Medical honey has a substantial efficacy on wound management and control of infection of pressure ulcer, as shown by low bacterial growth, decreased wound size, and improved healing stage [30].

Electric stimulation therapy (EST) accelerates pressure ulcer healing in SCI patients. Pressure ulcer healing is determined by decrease in wound size and improvement in wound appearance after 3 months of treatment with EST [31]. Use of ultraviolet light C (light wavelength 200–290 nm) may be effective in treatment. It can be because of its potency in killing antibiotic-resistant microorganisms. *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* that may be resident on superficial layer of wound may be killed by ultraviolet light C [32]. Maggot therapy may also be used a subsidiary way to treat wound ulcer. Live blowfly larvae in wound dressings accelerate wound healing by increasing debridement. They can debride necrotic tissue within 1 week that is so rapid in nonsurgical wound management. It is safe, simple, and inexpensive, and it seems that it has no complications, so it can be used for treatment of pressure ulcers in SCI patients [33].

### *2.2.3. Prevention*

Pressure ulcers certainly have a great influence on daily activity and life of SCI patients [34]. The best position and the turning frequency are not clear, but avoiding the 90° lateral position is recommended. This position will bring about high pressure over the trochanters with

the risk of pressure ulcer development. The risk of developing pressure ulcer is highly individualized and the SCI patient is at a significant risk. Prevention strategies in seating position and in bed are very important in this group to prevent pressure ulcer, and so, pressure relief maneuvers can be important [35]. Pressure relief, position changes, and regular and frequent observation of skin, especially on the pressure areas, that is, over the bony prominences can prevent pressure ulcer development [2]. Pressure ulcers can also be prevented by improvement of neurologic functions and reducing the time of hospitalization and rehabilitation stay [36]. Pressure ulcer prevention is strongly associated with lifestyle modification [35]. Frequent change of position and use of pressure-relieving devices have important roles in reducing the pressure ulcer development. Some risk factors other than pressure may be important in developing ulcer. In SCI patients who do not have vasomotor control below the level of the lesion, hypoxemia will develop, and it can be an important risk factor. So, pressure ulcers may be prevented not only by reducing external pressure by pressure relief, but also by increasing the patient's resistance to pressure, by increasing tissue oxygenation [37]. One of the important risk factors that may increase skin and soft tissue infections is resistant bacterial colonization. Some activities such as hand hygiene, contact precautions, and cultural changes are associated with significant declines in bacterial infection, especially MRSA colonization and infection [28].

### 2.3. Osteomyelitis

One of the complications of spinal cord injury is osteomyelitis. Osteomyelitis may develop by extension of infection from pressure ulcers [38]. After spinal fixation surgery, osteomyelitis may be developed, as a complication of surgery. Osteomyelitis increases the treatment cost and may lead to other complications [39].

#### *2.3.1. Diagnosis*

There are several diagnostic methods for diagnosis of osteomyelitis in SCI patients.

Bone biopsy is the gold standard, and magnetic resonance imaging (MRI) is usually used as a sensitive and specific modality. Several organisms are known as causative agents. The most common isolated organisms are *Staphylococcus aureus*, Peptostreptococcus, and Bacteroides. Coagulase-negative staphylococci, group B Streptococcus, Proteus, and group milleri Streptococcus may also be isolated as less common agents. The diagnosis of pelvic osteomyelitis is difficult and may need multiple bone biopsies. At least three bone samples may be necessary to detect the pathogen and exclusion of contamination. In one study, sensitivity of MRI for diagnosis of pelvic pressure ulcer osteomyelitis was 94% and specificity was 22% [40].

However, Huang's study demonstrates that MRI is a sensitive method for diagnosis of osteomyelitis in SCI population. MRI can be used to demonstrate the extension of infection and to guide limited surgical resection and preserve viable tissue [41]. Pelvic pressure ulcers that accompany osteomyelitis may show cortical erosion and bone marrow edema in MRI [42]. In SCI patients, abscesses, fluid collections, and sinus tracts can be detected by MRI [43]. For diagnosis of osteomyelitis, gallium scan and plain pelvis X-ray may be used. Negative bone

scan can rule out osteomyelitis. However, chronic ulcers usually accompany osteomyelitis. Delayed healing or recurrence of pressure ulcers has no clear association with osteomyelitis [44]. Computerized tomography and Technetium-99 m bone scans are not usually used for diagnosis of osteomyelitis in SCI patients with pressure sores [45].

*2.3.2. Treatment*

Treatment of osteomyelitis is composed of two parts: surgical management and medical treatment. Surgical approach is in fact debridement and in some patients, muscle flap. Medical therapy is in fact antibiotic therapy and wound care. Hyperbaric oxygen may be used in refractory osteomyelitis [46]. Treatment of osteomyelitis is prolonged and so, expensive. Using surgical debridement can shorten the duration of antibiotic therapy for osteomyelitis in SCI patients. In SCI patients with bony prominence osteomyelitis, surgical debridement and flap coverage of the sore can influence the outcome of antibiotic treatment [47]. Antibiotics for treatment are chosen according to the results of culture.

*2.3.3. Prevention*

Measures for prevention of osteomyelitis are in fact those that were mentioned in Section 2.3.1 for prevention of pressure ulcer and skin and soft tissue infection. The main preventive measures are pressure relief, regular change of position, and frequent observation of the skin over bony prominences.

**2.4. Pneumonia**

Pulmonary complications in SCI patients are important, as they may be life threatening. Pneumonia, pulmonary infarction, pulmonary thromboembolism, chest injury, and atelectasis are the most frequent and important complications in these patients. Pneumonia is one of the most important pulmonary complications. It may have developed shortly after spinal cord injury, during hospitalization or even in rehabilitation periods. The risk of pneumonia is greater in post-injury period. In this phase, the patients usually do not have effective cough. If the phrenic and intercostal nerves have been damaged, the respiration cycle may be influenced and the patients may be prone to pneumonia [48]. After intubation and mechanical ventilation, ventilator-associated pneumonia (VAP) may develop. VAP is in fact the occurrence of pneumonia in patients with mechanical ventilation, occurring more than 48 h after endotracheal intubation [49]. VAP is the most frequent nosocomial infection in patients with mechanical ventilation and is associated with longer intensive care unit stay, longer duration of mechanical ventilation, and high morbidity and mortality [4].

*2.4.1. Diagnosis*

Pneumonia is diagnosed by signs and symptoms of respiratory infection and according to criteria for diagnosis of nosocomial pneumonia and VAP. By endotracheal culture, the causative organism is found and an antibiotic is chosen according to the result of culture. The most common organisms are *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Acinetobacter baumannii* [50],

*Serratia marcescens* [51] and methicillin-resistant *Staphylococcus aureus* [52]. Chest radiograph accompanied by clinical and laboratory findings are required for diagnosis of patients with suspected VAP [53].

#### *2.4.2. Treatment*

Antibiotics are chosen according to endotracheal secretion culture. For empirical treatment, combination antibiotic therapy is necessary. In this combination, an anti-pseudomonas agent (that is usually effective on other gram negative organisms) such as imipenem, meropenem, piperacillin-tazobactam or cefepime in addition to an aminoglycoside or a quinolone is used. For coverage of Methicillin-resistant *Staphylococcus aureus (*MRSA*),* vancomycin is usually added to this combination. For a special situation such as multidrug-resistant Acinetobacter or Pseudomona, the appropriate antibiotic (like colistin) is elected according to culture. The rising rates of antimicrobial resistance have led to the routine empiric administration of broad-spectrum antibiotics even when bacterial infection is not documented [52].

#### *2.4.3. Prevention*

One important risk factor for developing pneumonia is retained secretion. So, pulmonary toilet is important in these patients. Appropriate positioning and cough assistance can be useful for clearing retained secretions. Sometimes early intubation may be necessary to prevent secretion retaining by frequent suctioning [48]. Using effective oral care with antiseptics is associated with the reduction of the incidence of ventilator-associated pneumonia. Oral care solutions have been widely used to prevent ventilator-associated pneumonia [49]. Routine cleaning and disinfection of ventilators can play an important role in VAP prevention and management approach [53].

### 2.5. Other infections

Blood stream infection secondary to urinary tract infections, pneumonia, pressure ulcers [48], catheter-related bloodstream infections [54], and infections at other sites may occur in SCI patients. Meningitis may occur after penetrating injuries or as a result of CSF leakage at the time of injury or subsequent to surgery [48]. Epidural abscess and subdural empyema can be developed with the same mechanisms. Ventilator-associated tracheobronchitis (VAT) is an infective complication of mechanical ventilation and is a part of the spectrum of ventilator-associated respiratory infections [55].

## 3. Conclusion

Infectious diseases after spinal cord injury are important and should be considered in patients with fever and other signs and symptoms of infections. Appropriate approach, diagnosis, and treatment and surgical interventions, if needed, can be lifesaving and can decrease mortality and morbidity.

## Acknowledgements

With special thanks to Dr. Hadi Niknam, my dear neurosurgeon colleague, and Mrs. Shadi Nasrizadeh Moghaddam.

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Chapter 6

# Role of Gait Training in Recovery of Standing and Walking in Subjects with Spinal Cord Injury

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.71312

**Abstract**

Gait training has an important role in rehabilitation of standing and walking in spinal cord injury (SCI) patients. There were different types of gait training in these subjects. Both the body weight support treadmill training and robotic-assisted and robotic exoskeleton are effective and secure methods for gait training and improving the energy demand and metabolic cost in SCI patients in different level of injury. The powered exoskeletons can provide patients with SCI the ability to walk with the lowest energy consumption. The powered exoskeleton's energy consumption and speed of walking depend on the training duration. Based on different types of gait training methods, training time, and other affected parameters, the aim of this chapter was to evaluate the role of gait training in recovery of standing and walking in SCI patients.

**Keywords:** spinal cord injury, gait training, standing, walking

## 1. Introduction

The act of learning how to walk (as a child, or more frequently, after sustaining an injury or disability) is so-called **gait training** or **gait rehabilitation**. In this chapter, we focus on gait training after spinal cord injury (SCI). The purpose of gait training for subjects with SCI is usually to increase walking endurance and to decrease subject's dependency. Standing and walking can help to prevent contractures of the lower limb joints, as well as osteoporosis, spasticity, bed sores and edema, complete discharge of bladder, and prevention of bladder infection in subjects with SCI [1–4].

Spinal cord injury is spinal cord damaging that causes changes in function, most frequently and importantly, disruption in lower limb motor and sensation. Inability to walk is the most

important limitation for affected patients [5]. Among lots of serious problem which patients encounter with, but after injury the first question is "will I ever walk again?" [6]. As a result, retraining the affected patients to achieve walking ability is important.

The main determinants of normal gait are [7]:

- Stability and posture,
- Range of motion (ROM),
- Muscle strength,
- Co-ordinated motor control,
- Muscle tone,
- Proprioception,
- Vision,
- Cognition,
- Aerobic capacity out of which the first six factors are impaired in spinal cord injured individuals.

In patients with SCI, there are no main determinants of normal gait, but in recent years, there have been advancements in how the patients can increase the ability to walk. Rehabilitation procedures should focus on the development of outcome by using the neuroplasticity and by using a functional training.

Lovely et al. in 1990 demonstrated neuronal circuits below the level of lesion become activated by an appropriate afferent input. They established that stepping practice plays an important role in training [8]. When the practice of stepping is accomplished, walking can be done more effective than when it is not practiced. In spinal cord, when a motor task wants to be recognized in neural circuit, it should be practiced appropriately and sufficiently. The name of this process is training [9]. De Leon et al. in 1998 and Wirz et al., 2001 stated that appropriate afferent input activate neuronal networks below the level of injury in a SCI patients, and activated neural network generate electromyography activity for suitable function (even in complete SCI without supraspinal input) [10, 11]. Dietz et al. in different experiments in human and animals revealed externally assisted walking, with tools and equipment or therapist, when appropriate afferent input will drive to spinal cord, a locomotor pattern will train and muscle activity (EMG) will be turned on even in complete SCI; however, muscle activity in complete SCI is low in comparison with healthy subjects but muscle EMG will increase by practicing more and more during training sessions [12].

One of the important afferent inputs is foot load receptor input. Researchers perceive the importance of these kinds of afferent input when they use externally assisted walking while patients are unloading. In this experiment, they understand unloading does not activate muscle EMG activity and they claim that, body unloading and reloading are considered to be of crucial importance to convince training effects upon the neurological locomotor centers,

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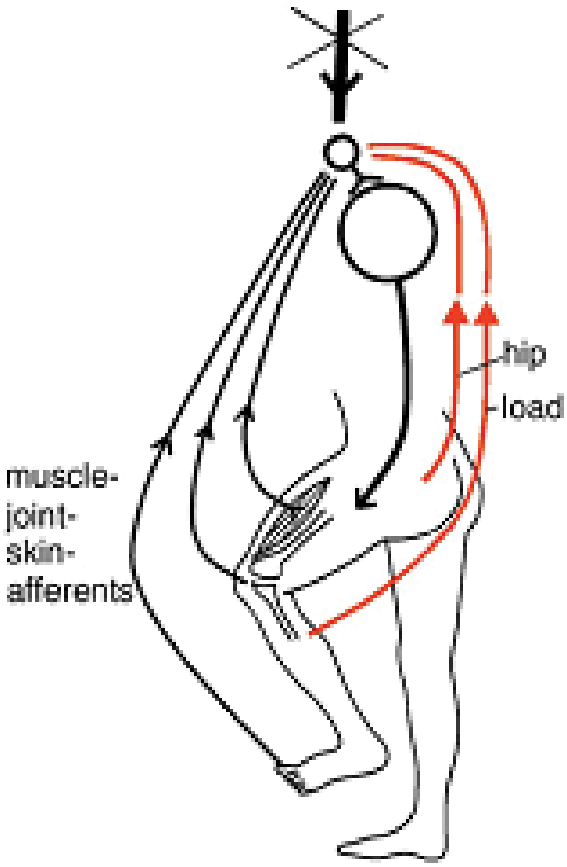


**Figure 1.** Schematic drawing of the afferent input from load- and hip joint [14].

because the afferent input from foot pressure during the stance phase is essential for the activation of spinal neuronal network (**Figure 1**) [13]. Dietz in 2008 suggested that another important input after foot contact pressure is proprioceptive input from extensor hip muscles. Foot sole mechanoreceptor with hip extensor muscles proprioception provides load information (**Figure 1**) [13].

## 2. Gait rehabilitation interventions following spinal cord injury

Until now, many therapeutic strategies have been developed for promoting locomotor activity of SCI subjects ranged from those that compensate for weakened or lost function (e.g. orthotic gait training) to strategies based on the concepts of central nervous system (CNS) plasticity (e.g. Erigo therapy and body weight–supported tread mill training) [15, 16]. Strategies that are based on the concept of CNS plasticity have shown improvement and enhancement in walking ability of SCI subjects through implementing the task-specific sensory input and repetitive and intensive gait therapy [17, 18]. These strategies will be explained as following.

## 3. Early gait rehabilitation interventions after spinal cord injury (Erigo therapy)

SCI subjects, in acute stages, are disposed to orthostatic hypotension occurrences while transferred from a horizontal to an upright position due to the lack of sympathetic activity and also leg muscle contractions that finally lead to delay in starting the functional gait training [18, 19]. On the other hand, the mobilization and verticalization of SCI patients in acute care with limited or no capacity for cooperation can be very challenging. One approach to decrease the orthostatic hypotension incidences is utilizing tilt table. Many limitations related to the use of traditional tilt table have been reported such as no leg movements, limited training duration due to the lack of patient's cardiovascular stability and excessive labor load on therapist for passive movements. Therefore, for overcoming of such limitations a novel, robotic tilt table so-called Erigo was designed and developed, which offered a locomotion therapy at a very early stage of rehabilitation. These types of approaches through utilizing a safe mobilization and intensive sensorimotor stimulation, ambulates the lower extremity, and suggests a wide range of positive impacts and functions to enhance early rehabilitation of SCI patients [18–20].

The design and construction of the "Erigo" was based on the conventional tilt table but combines gradual verticalization plus robotic leg movement's therapy and functional electrical stimulation [18] (**Figure 2**). The main superiority of "Erigo" to the traditional tilt table was utilizing the robotic leg movement and the cyclic leg loading that produce critical afferent stimuli for the central nervous system [18, 20, 21]. These afferent stimuli result in muscle activation, improved muscle pump function and venous return, which eventually result in improved cardiovascular stability in SCI subjects. There are a few studies about the efficacy of "Erigo" following spinal cord injury [18, 22, 23]. According to the previous research by Colombo et al., using Novel tilt table (tilted to 60° upright position) in five subjects with complete SCI (ASIA impairment scale A between C4 and C7) resulted in the increase of blood pressure and after stopping the automated movement, the mean arterial pressure decreased statistically significant($P < 0.0001$) [14]. Although this study showed the positive effects of passive movements of leg through using "Erigo" therapy on circulatory system in SCI patients, it has to be stated that further studies are necessary to test this type of approach in a larder patients group of SCI with different level of injury and also in the long term to indicate the direct effects of "Erigo" therapy.

Also Laubacher et al. indicated that the "Erigo" therapy is practical for respiratory and cardiopulmonary training and evaluation of incomplete SCI subjects and they found it was a tolerable and implementable approach [22]. Another approach in the rehabilitation of SCI subjects is combining the tilt table with vibrating foot plates (whole-body vibration) that focus on the activation of muscular and vascular systems. Herrero et al., found that whole body vibration (WBV) is an effective approach to enhance leg blood flow and to stimulate muscle activity in SCI subjects; therefore, they concluded that this approach could be incorporated in the rehabilitation programs of SCI subjects. So in future studies, we need to compare the efficacy of Erigo therapy and whole body vibration (WBV) on orthostatic, blood pressure, and EMG in subjects with SCI [24].

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**Figure 2.** Erigo components.

Also integrating functional electrical stimulation (FES) into "Erigo" provides more physiological and clinical benefits (**Figure 3**). The nerve endings are stimulated through attaching electrodes to the skin, which results in contraction and activation of muscles. Many positive effects have been reported by using of "Erigo" plus FES like improving in the cardiovascular system and metabolism condition, decreasing spasticity, improving the muscle tone, reducing long-term consequences due to the lack of muscle activity, inducing functional movements, increasing cardiovascular stability during upright position, and promoting the orthostatic tolerance by enhancing venous return in individual with SCI [18, 22, 25, 26]. Thrasher et al. compared the effects of isometric FES and dynamic FES on cardiovascular parameters on an active tilt-table stepper in 16 young and healthy adults. They stated that isometric FES led to short-term increases in blood pressure and also heart rate, but dynamic FES maintained increase in blood pressure over the long term. They postulated that however FES has potential to counteract orthostatic stress it should be combined with movements of leg [27]. In a pilot study, Yoshida et al. found that through applying FES cyclically to the leg muscles of 10 SCI subjects at T6 or higher, they could better retain their blood pressure. Although FES and

**Figure 3.** Functional electrical stimulation synchronized with leg cycling in "Erigo".

passive stepping by Erigo achieves this function by inducing venous return, passive stepping was less effective than FES in this study [23]. Finally, many studies are needed to extend these findings to the community of people with SCI with different levels of injury.

## 4. Body weight–supported treadmill training approaches after spinal cord injury

The most outstanding strategy for regaining the walking ability in SCI subjects is body weight–supported treadmill training (BWSTT) [16, 26, 28]. Traditionally, BWSTT device supported some of the SCI patient's body weight by using a harness, as therapists manually assist their legs via the stepping movement on a treadmill. Although, it has been shown that such interventions could enhance and promote locomotor activity in SCI subjects, according to the previous researches, traditional gait therapy had many disadvantages such as excessive labor load on therapists, confined training duration, and gait pattern without any feedback for patients (**Figure 4**) [17]. Therefore, body weight–supported treadmill training using lower extremity robotic exoskeleton (e.g. Lokomat) was designed and developed and initially implemented for SCI rehabilitation. The BWSTT with robotics exoskeleton has originated from the central pattern generator (CPG) and is a secure and functional intervention that allows gait training by covering the limitations of conventional gait therapy [16, 29].

One of the famous robotics exoskeleton use in conjunction with the BWSTT is the Lokomat (Hocoma AG, Volketswil, Switzerland), which is a bilateral robotic orthosis, worn by patients, and attaches to a treadmill frame to provide powered assistance at the hip and knee in the sagittal plane, while a therapist can check the system and regulate assistance as necessary (**Figure 5**) [17, 28].

The Lokomat has been demonstrated to be effective in producing more normal walking patterns and promoting walking ability in subjects with incomplete SCI. Generally, applying the robotic

http://dx.doi.org/10.5772/intechopen.71312

**Figure 4.** Traditional BWSTT (A) V.S. BWSTT plus robotic exoskeleton (B).


**Figure 5.** Lokomat components.

exoskeleton device in conjunction with the BWSTT, in gait rehabilitation procedure, could potentially accelerate recovery of walking ability in individual following SCI through enhancing the duration of training and reducing the labor load on physical therapists [17, 28, 29].

## 5. Orthotic gait training

There are different types of orthoses and assistive devices for standing and walking in complete and incomplete spinal cord injury subjects [30]. This type of intervention ranged from solid ankle foot orthosis to reciprocating gait orthoses and powered gait orthoses, which

were used to low incomplete level of spinal cord injury and high complete or incomplete level of injury [31]. In general concept, all orthoses were used with walking aid for ambulation. Several factors influenced the providing walking ability via orthoses in the SCI subjects, which gait training is the important of them [32].

## 6. Orthotic gait training of SCI subjects with the mechanical orthoses

There were different types of mechanical orthoses such as hip-knee-ankle-foot orthosis, reciprocating gait orthosis (RGO) (**Figure 6**), hip guidance orthosis, and medial linkage orthoses (e.g. walkabout orthosis (WO), Primewalk orthosis (**Figure 7**)) to provide standing and walking in subjects with SCI [30]. Several studies evaluated this type of orthoses on walking ability in these subjects [30]. Based on the evaluation of the energy expenditure, Harvey et al. demonstrated that energy consumption of walking with the WO were greater than walking with the isocentric reciprocating gait orthosis (IRGO) in SCI subjects with T9–12 paraplegia [33]. In addition in another study, Harvey et al. demonstrated that stand up and sit down with WO was easier than IRGO, but IRGO provided faster and more independent ambulation [34]. In comparison of the attitude of subjects with SCI when using WO and the IRGO, Harvey et al. reported few

**Figure 6.** Isocentric reciprocating gait orthosis [32].

**Figure 7.** Walkabout orthosis and Primewalk orthosis.

subjects used orthosis more than once every 2 weeks, and SCI individuals were primarily wearing the orthoses for therapeutic aims [35]. To evaluate the influence of Primewalk orthosis and walkabout orthosis in improving the walking performance in subjects with SCI, Ongio et al. demonstrated the Primewalk orthosis had better effect in walking efficiency than that of the Walkabout orthosis [36].

Training time announced different in this field between 2 until 12 weeks. Longitudinal training program demonstrated the better results on the improvement of walking parameters. The maximum rate of the speed of walking reported from 0.13 to 0.63 m/s, which is 13–57% of the optimal speed (1.1 m/s) required for successful community ambulation [37]. Home or indoor mobility for exercise, upright posture, and standing reported final benefits of orthotics gait rehabilitation [38, 39].

The successful orthotic gait rehabilitation in SCI subjects related to the several factors included well-motivated, with complete level of injury at T9 or below, incomplete level of injury, postural control, and [39–41] good upper extremity strength, as well as less spasticity and low level contractures [42], reduced thoracolumbar mobility, back pain, or any musculoskeletal problems that influenced standing upright [33, 43]. Orthotic gait rehabilitation can be influenced by the acceptance of orthoses. In other words, acceptance of orthoses may be influenced by donning and doffing time, the best time for donning and doffing of orthosis should be less than 5 minutes [31].

## 7. Orthotic gait training of SCI subjects with powered gait orthoses

Providing gait training in different environments such as clinic, home, or community announced as the main benefit of wearing powered gait orthosis [3]. Only limited PGOs are currently commercially available to the public and therefore would be able to be used

**Figure 8.** The HAL-5 type-C (hybrid assistive limb).


**Figure 9.** The ReWalk powered orthosis (Argo Medical Technologies).

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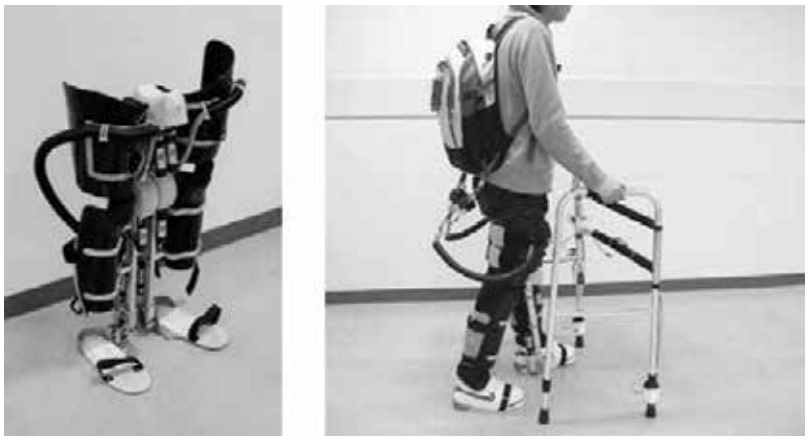

**Figure 10.** The wearable power assist locomotor.

in the field in SCI subjects. The concept of using PGOs is the reduction of energy demand in uses and reduces loads on the upper limb joints.

The HAL-5 Type-C (hybrid assistive limb) (**Figure 8**), the ReWalk powered orthosis (Argo Medical Technologies) (**Figure 9** ), the wearable power assist locomotor (**Figure 10**), and the eLEGS-powered orthosis (Berkeley Bionics) (**Figure 11**) are commercially powered orthoses for ambulation in SCI subjects.

In the evaluation of the gait training with the HAL-6LB on the SCI subject for 8 days, for 2 hours per day, Tsukahara et al. reported that walking speed and cadence were 0.11 m/s and

**Figure 11.** The eLEGS-powered orthosis (Berkeley Bionics).

20 steps/minutes, respectively [44]. In the evaluation of Rewalk exoskeleton on safety and tolerance in SCI patients, Zeilig et al. reported that mean time to walk 10 m was 47 seconds following training when using the Rewalk [45]. In another study, distance walked for 50–100 m announced between 5 and 10 minutes continually. The mean walking speed was 0.25 m/s [46]. In the evaluation of the wearable power assist locomotor orthosis (WPAL) on walking, physiological cost index (PCI) and muscle activity of the upper extremities in SCI subjects, Tanabe et al. reported all patients walked independently with the new powered device. The increased walking duration and distance of walking and reduction of the PCI and muscle activity of upper limbs with the WPAL compared to that the Primewalk orthosis [47]. Based on the literature in this field, we can conclude that PGOs can enable safe walking and reduce energy expenditure compared to mechanical orthoses in SCI subjects.

## 8. Orthotic gait training with hybrid system (bracing combined with FES) in SCI

High level of energy demand and high effort and loads on the upper limb joints announced the main complication of the orthotics gait rehabilitation with mechanical orthoses. Combination of the mechanical orthoses and FES innovated to improve gait parameters and reduce the loads and energy demand in SCI subjects. The main concept of the using this type of approach announced trunk and hip stability and facilitate forward progression.

Different studies in this field evaluated the hybrid systems on the walking capacity in SCI subjects [38, 40, 48, 49]. Distance walked was announced as 180–1400 m in these studies [38, 40, 48, 49]. Although there was no significant improvement in the walking speed, but improvement in the distance walked was observed in trails in this field. The rate of the distance walked was announced between 3 and 400 m when the FES or orthoses were trained alone [38, 40, 48]. In subjects with incomplete level of spinal cord injury, the gait training with hybrid systems provided improvement in ambulation capacity compared to bracing or FES using alone [50].

## 9. Orthotic gait training protocol

The training approach announced different among the studies on SCI population [51]. Training protocol has been performed different for powered and mechanical orthoses. Based on the time of the training program, five studies had a shorter training period [26, 45, 52–55], while several weeks to months were reported in other studies [32, 51]. Training protocol was being done on the different surfaces including sidewalk, grass, or stairs [56–58]. Yong et al. used the training protocol with powered gait orthosis on the treadmill to increase confidence of SCI subjects and improvement of the walking speed on them [59]. While in using powered gait orthosis, Arazpour et al. [60] performed upper extremity strengthening and lower extremity stretching as the main section of the training during orthotic gait rehabilitation. Further study on how different training programs affected the walking ability outcomes in the SCI patients will be beneficial in this field.

Orthotic training in SCI subjects can be reduced fatigue and fear of falling and increased the stepping [61]. It was announced that after training program, SCI subjects had walking ability and performance of activity of daily living. The SCI subjects may have less energy demand during walking with orthoses compared to without orthotic gait training condition [32].

## 10. Positive results of walking in SCI subjects

Complications of SCI such as spasticity, joint contractures, pressure sores, osteoporosis, and urinary tract infections may be present in subjects with SCI [1, 2]. Standing and walking provides physiological and psychological benefits for individuals with SCI [3]. A reduction of bed sores, osteoporosis, spasticity, contractures, and improvement of bladder and bowel functions have all been announced after standing and walking in subjects with SCI [1, 4]. Orthotic gait training is the intervention, which can help in SCI subjects.

Future study in this field must be focused on the following terms:

- The effect of orthotics gait training on the quality of life in SCI subjects
- The effect of orthotics gait training on the electromyography of the lower limb muscles
- Comparison between orthotics gait training with RGOs and powered orthosis on the walking parameters and other related parameters

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Chapter 7

# Cellular Transplantation-Based Therapeutic Strategies for Spinal Cord Injuries: Preclinical and Clinical Updates

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73220

**Abstract**

Spinal cord injury (SCI) is a distressing neurological condition that causes loss of neural tissue, with subsequent damages to neural circuitry, and loss of sensorimotor function. The SCIs have an estimated incidence rate of ~80 cases per million populations. Till date, no ratified effective therapeutic strategy for SCIs exist; however, recent advancements in regenerative medicines to protect and regenerate damaged/lost neural tissues following SCIs have shown promising results in preclinical and clinical trials. Moreover, there is a greater need to fully understand underlying mechanisms following cellular transplantation that can be achieved through proper differentiation of desired cell type, and their *in-vivo* tracking of migration, proliferation and integration into the host system. Furthermore, techniques that can prevent teratomas formation following cellular transplantation have been reported. In addition to the ongoing comprehensive neuroregenerative and neuroprotective therapeutic strategies for SCIs, novel technologies are emerging including neuroscience-based computational and robotic rehabilitational therapies. These improved strategies in combination with cell-based therapeutic approaches are opening new avenues for future research to completely cure SCIs. Herein, we intended to review pathophysiological mechanisms following SCI, preclinical and clinical updates of cellular transplantation, the extent of success from these transplantations, associated controversies and other emerging technologies.

**Keywords:** spinal cord injury, pathophysiology, stem cells, preclinical and clinical trials, regenerative medicines, neuromodulation, robotic rehabilitation

## 1. Introduction

Spinal cord injury (SCI) is an extremely devastating condition with no proper effective treatment strategies till date. Instead of all the recent comprehensive research, SCIs still remain as one of the most intimidating challenge in the field of neurological sciences [1]. The increasing prevalence of SCIs specifically in young generation has caused a serious clinical, social and economical burden across the globe. According to a report by World Health Organization, SCIs has affected people worldwide with an estimated incidence rate of ~80 cases per million population [2]. The causes for SCIs could be a result of traumatic (~90%) or non-traumatic (~10%) events. Although the percentages of traumatic SCIs are high, recently it has been estimated that percentages of non-traumatic SCIs are also increasing majorly due to spinal cord tumors [2, 3].

Following SCIs, severe damages to the neural tissue occur followed by further damages to the neural circuitry, which results in loss of sensorimotor functions [4]. So much of the pathophysiological events cause serious failures in body system that makes it harder or nearly impossible to treat. In addition to neurorehabilitation, the highly established therapeutic strategies for SCIs focus on protocols that can induce early neurological protection and prevent secondary SCIs. While these procedures have revealed to encourage locomotional recovery in affected individuals with incomplete SCIs, the therapeutic outcome in patients with life-threatening incomplete and complete SCIs continues to be disappointing [5]. These kind of therapeutic failures are due to the deficiency of natural regeneration of injured axons where demyelination has occurred. Till date, various number of significant *in vivo* studies that are predominantly experimented on the model of mammalian SCIs in the recent years have contributed to the establishment of several regenerative approaches including neuroprotective therapeutics-coupled regeneration and cellular transplantation with neurotrophic activity. In this review, we are intended to cover pathophysiological mechanisms following SCI, preclinical and clinical updates of cellular transplantation that majorly involve cells population derived from human embryonic stem cells (hESCs), mesenchymal stem cells (MSCs) and human-induced pluripotent stem cells (iPSCs), the extent of success from cellular transplantation, associated controversies and other emerging technologies.

## 2. Global prevalence of spinal cord injuries

According to World Health Organization (WHO) report, individuals suffering from SCIs hold 2–5 times more chances of premature death compared to non-SCI individuals, whereas the ratio of survival rate get worsen in low and middle income countries [2]. The high morbidity ratio of SCIs has driven widespread exploration into treatments and rehabilitations to recover neural function after SCIs. The incidence and prevalence rate of SCIs, in particular of traumatic SCIs, varies widely among different regions across the globe, mainly due to fluctuating sources of facts and figures and missing or unrecorded data [6]. Apart from including sudden deaths from SCIs, the annual incidence rate of traumatic SCIs across the globe is 2.5–83 cases/per million

population, whereas the highest ratio has been recorded in the USA [6]. Although the incidence rate of traumatic SCI is high, recently it has been reported that the incidence rate of non-traumatic SCIs is also increasing [5]. According to WHO report, there are around 250,000–500,000 people suffering annually from SCIs across the globe, where majority of the cases are due to road vehicle accidents, tumbles and other physical aggressiveness. As per 2016 updated report from National Spinal Cord Injury Statistical Center (NSCISC), the estimated annual incidence rate of SCI is ~54 cases/million population. The estimated number of individuals living with SCIs in 2016 is ~282,000, whereas the ratio is higher in male population accounting for around 80% of newly reported cases of SCIs [7].

## 3. Pathophysiology of spinal cord injuries

A comprehensive understanding of the neuropathological alterations after a SCI is the crucial part in designing effective therapeutic strategies. The SCI is primarily due to either compression or contusion [8]. The fundamental mechanisms that are involved in initial and later stages of SCIs include vascular complications, inflammation, lipid peroxidation, demyelination and apoptosis [9].

### 3.1. Vascular disorders

Ischemia, hemorrhage, systemic hypotension and microcirculatory disturbances are the vascular manifestations due to SCI [10]. The major decrease in blood flow at the lesion site occurs immediately after SCI [11], while the ischemia becomes worsen in the first few hours [9]. After a period of ischemia, blood reperfusion occurs with increased free radicals that lead to reperfusion paradoxical damage [12]. The disruption of small blood vessels and hemorrhage affects more of the local microcirculation than the large arteries, which leads to a failure of glutamate-mediated excitotoxicity and autoregulation. Additionally, severe systemic hypotension increases the microcirculation dysfunction and exacerbates injury [13].

### 3.2. Inflammation

After a SCI, the perniciousness from inflammation to the nervous tissue influences the cells to get into necrosis in the injured site. At this stage, different immune cells, including neutrophils, monocytes, microglia and T-lymphocytes, secrete certain cytokines such as tumor necrosis factor-$\alpha$, interleukin-1$\beta$ and interleukin-6, which lead to apoptotic cell death [14]. First, the neutrophils aggregate at the damaged area and release cytokines, proteases and free radicals that lead to more inflammation while involving glial cells in the inflammatory process, which eventually induce cell death [9]. This is followed by the infiltration of monocytes into the injury site, which is followed by differentiation into macrophages. The monocytes and a recently triggered microglia secrete cytokines, free radicals and growth promoting factors. The T-lymphocytes secrete neurotrophins and modulate microglia to protect neurons from degeneration [15].

### 3.3. Glial-associated damage

In SCI, damage to the myelin sheet that is demyelination causes the exposure of axons to the harmful surroundings that lead to necrosis or apoptosis of overall neurons [9]. Moreover, the process of demyelination delays or blocks signal conduction via axons that leads to ineffective communication between neurons. This process of demyelination is a result of damages to the oligodendrocytes that were generated by glutamate excitotoxicity [16]. Later on, an inflammatory reaction regresses, which is followed by a formation of glial scars. In the initial stages of SCI, astrocytes proliferate at the damaged site to form glial scars, which separate neural tissue to decline neuroinflammation in early phases. Cells in this scar region secrete inhibitory molecules, which inhibit functional recovery [17].

### 3.4. Necrosis and apoptosis

In the initial stages of SCI, neurons, microglia, oligodendrocytes and astrocytes undergo apoptosis and necrosis, while in later stages apoptosis is mostly limited to white matter [18]. In majority of cases, the SCI results in calcium influx and increased excitotoxicity, which are the major triggers for apoptosis and mitochondrial dysfunction [19].

### 3.5. Lipid peroxidation

Lipids are abundantly found in tissues of CNS and PNS, which indicate that spinal cord is more vulnerable to lipid peroxidation that can lead to lysis of cell membrane [9]. Since free radicals are abundantly present in injury site, increases in their level will eventually lead to lysis of cell membranes via lipid peroxidation. Consequently, mitochondrial dysfunction occurs as a result of oxidative damage and induces calcium overload [20]. The calcium influx causes ion imbalance and excitotoxicity, which is triggered through acute SCI [9]. Additionally, high level of glutamate is released after SCI, which results in increased calcium influx and damage to the spinal cord by stimulating the AMPA and NMDA receptors that induce neuronal death by apoptosis or necrosis [21]. The oligodendrocytes and neurons are susceptible to glutamate excitotoxicity as they express glutamate receptors [3]. Consequently, excitotoxic injury induces axonal demyelination. Additionally, nitrous oxide is involved in glutamate excitotoxic injury [22]. The increased calcium ions level has a major role in the secondary injury mechanism.

## 4. Molecular alterations involved in injured spinal cord

An advanced physiopathology induced by SCI affects the cellular growth and overall integrity of nervous system by comprehensive and progressive molecular pathways [23]. The initial stages of SCI are recognized by higher expression of genes mostly involved in inflammation and lower expression of genes involved in tissue architecture and neuronal signal transduction. The later stages of SCI are characterized by upregulation of proteins involved in angiogenesis, cell growth, axon guidance and reformation of extracellular matrix. Other molecular

mechanisms that support the struggle of tissue survival after SCI include higher expression of proteases and stress proteins and lower expression of cytoskeletal and synapsis-based messenger RNA [14]. Following are the molecular alterations after SCI.

### 4.1. Stress and transcription response

At the initial stage of SCI, different cellular factors such as nuclear factor kappa B (NF-κB) and 70 kD heat shock protein (HSP-70) get activated that last for 24 hours. A stimulation of NF-κB facilitates more expression of genes to moderate regeneration or apoptosis [24]. Moreover, an increased level of HSP-70 with metallothioneins 1 & 2 protects the cells from oxidative stress. An activation of catalase, superoxide dismutases and glutathione peroxidase occurs in later stages [25].

### 4.2. Inflammatory reaction

During an early phase after SCI, interleukins (IL-6, IL-1β), cyclooxygenase (COX)-2 and TNF-$\alpha$ are activated, which get to normal stage again after 2 weeks. Integrins, vascular and intercellular CAMs, selectins and cadherins are upregulated in early phase of SCI [25]. Inflammatory genes are expressed in several spinal cord cells, which are predominantly studied in microglia. The interleukins IL-6, IL-1β and chemokine ligands, such as 2/M1P2$\alpha$ and 2/MCP-1, help in bringing different immune cells to the injured area [14]. After 3–7 days, microglial gene expression that includes genes, such as *MRF-1* (microglial response factor-1), *cathepsin*, *galectin-3*, *CYBA* (cytochrome b-245, alpha polypeptide), *CASP1* (caspase 1), *MAPK14* (mitogen-activated protein kinase 14), *CCND1* (cyclin D1) and leukocyte surface antigen *CD53*/*OX44*, contributes in immune response, phagocytosis and cell death. Furthermore, other genes such as the classical complement pathway, which related to phagocytosis, showed an insistent upregulation after SCI [25].

### 4.3. Neuron-related genes

A great number of genes that encode specific proteins for calcium, sodium and potassium pumps, synapsis and cell excitability show a major decrease in the first week following SCI [26]. This reduction reflects alterations of gene profile in neurons and the progress of apoptosis that occurs after SCI. Late axonal regeneration after SCIs is accompanied by overexpression of *CORO1B* (Coronin, actin binding protein, 1B), *RAB13* (Rab13, member RAS oncogene family), *NINJ* (Ninjurin), *ANK* (Ankyrin), cAMP-related genes and myelin oligodendrocyte glycoprotein [27].

### 4.4. Cell cycle genes

The upregulation of cell cycle genes, including *cyclins, c-Myc* (V-myc avian myelocytomatosis viral oncogene homolog) and *GADD45A* (growth arrest and DNA damage-inducible, alpha), is being reported after 24 hours of SCI [27]. Once these genes are activated, it induces apoptosis and astrocytic proliferation through formation of the glial scar [27]. In the initial stages of SCI, upregulation of associated genes, such as *BAX* (BCL2-associated X protein),

*BAK-1* (BCL2-antagonist/killer 1) and *CASP3* (caspase 3, apoptosis-related cysteine peptidase), is being reported. In later stages, the upregulation of *STAT3* (signal transducer and activator of transcription 3 (acute-phase response factor)) and *PI3K* (phosphoinositide 3-kinase) and downregulation of *GSK-3* (glycogen synthase kinase 3) are being observed [25]. In addition, earlier upregulation of genes that are involved in preventing apoptosis such as *PDGF* (platelet-derived growth factor), *TGFB* (transforming growth factor-β), *VEGF* (vascular endothelial growth factor) and anti-apoptotic proteins is being reported [24].

### 4.5. Glial cell alterations

There are well-recognized genes, such as *GFAP* (glial fibrillary acidic protein), *NES* (nestin) and *VIM* (vimentin), that are overexpressed in astrocytes and are found responsible for glial scar formation. They are found upregulated early after SCI [26]. In oligodendrocytes, the gene expression decline due to oligodendrocytic death, while an increase in myelination occurs in later stages [26].

### 4.6. MicroRNAs

MicroRNAs (miRNAs) have been recognized to play crucial roles in regulating growth signals and immune response [28]. Following SCI, microRNAs play important role in inflammatory pathways or in the invading immune cells. Soon after the SCI, damaged area is infiltrated with blood immune cells [29]. MicroRNAs control upregulation of vascular cell adhesion molecule (*VCAM1*)-mRNA [25] with downregulation of miR-126 [30]. Neutrophil infiltration clarifies upregulation of miR-223 [31], while overexpression of lymphocyte-specific miR-142 [26] associates with the aggregation of immune cells in the injured site during initial days [32]. Moreover, miRNAs are associated with microglia and macrophages activation. Mainly, the downregulation of miR-124 is associated with microglia by directing CCAAT enhancer-binding protein alpha (*CEBPα*), which is a principal transcription factor vital for myeloid cells development [33]. After SCI, MiR-124 shows a constant downregulation that causes microglial activation [32]. Other associated roles of miRNAs during different mechanisms of SCIs have been recently reviewed in [34].

## 5. Types of cells used in transplantation for spinal cord injuries

The use of cellular transplantation in SCIs has been reported to encourage regeneration of neural circuitry and recover the associated compromised function of nervous system. Transplanted cells are being observed to perform this job via secretion of indulgent neurotrophic factors at the injury site to boost the reformative capability, followed by developing a scaffold for axonal regeneration, myelination and replacement of damaged nerve cells [35], as depicted in **Figure 1**. Following are the type of cells that have been shown success in preclinical trials and currently being evaluated in clinical phase trials for treatment of SCIs.

http://dx.doi.org/10.5772/intechopen.73220

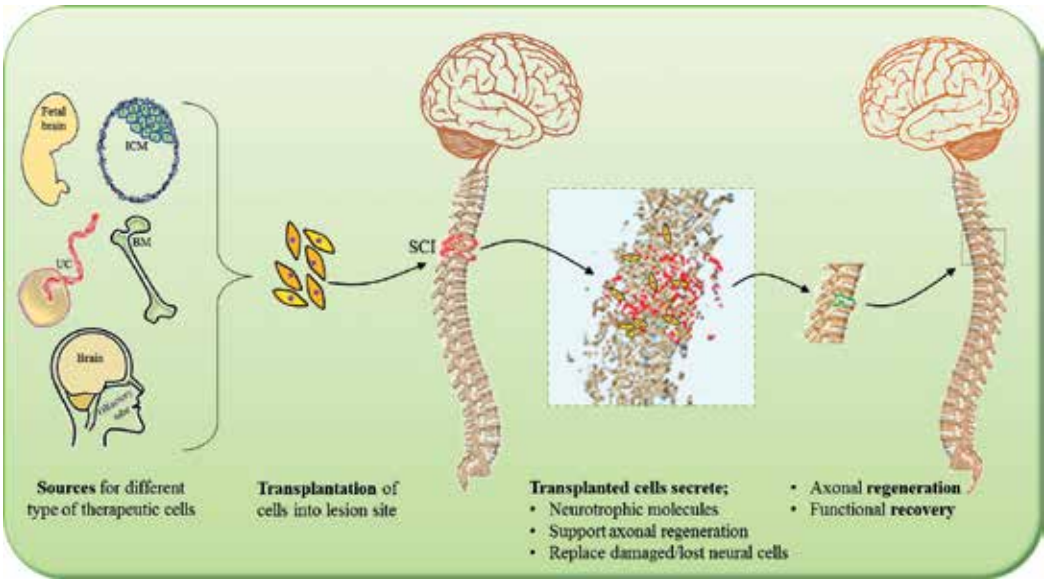


**Figure 1.** Graphical representation of cellular transplantation and functional recovery from SCI. Therapeutic cells are derived from different types of sources. Following cellular transplantations into injury site, the transplantable cells secret indulgent neurotrophic molecules to boost the regenerative capability, support axonal regeneration and myelination and replace damaged/loss neurological cells, resulting functional recovery from SCI.

### 5.1. Embryo-derived cell population

Although ethical issues are associated with the origin of embryonic stem cells (ESC), their potential use might significantly results into numerous scientific and clinical applications, especially if they are differentiated into desired cell types and are utilized to develop functional body organs [36]. The ESCs have been considered as a leading candidate of therapeutic cells for numerous types of disorders triggered by loss of cells/tissue or any abnormal body function [37]. A gap that has been produced in spinal cord after traumatic or non-traumatic injury can be refilled via new cell transplantation. To date, embryonic stem cells are considered as the most appropriate type of cells that can be used for this purpose. These are the immature cells that can differentiate into any of a cell type in human body including the cells of CNS and PNS. ESCs have been reported to form a bridge across the injury site, as well as they are capable of excreting neuroprotective factors that reduce the harmful effects from inflammation [38–40].

#### *5.1.1. Human embryonic stem cell-derived oligodendrocyte progenitors (hESCs-ODPs)*

Since the major problem associated to SCIs is "demyelination," a potential treatment option to replace the myelin-forming cells will be of significant interest. For this purpose, a transplantation of hESCs-ODPs into SCI rat model has shown to increase remyelination and promoted improvement in recovery of locomotory function [41]. This study paved the ways for the use of hESCs-ODPs for treatment of SCIs and supported the notion that pre-differentiation of hESCs into active oligodendrocytes progenitors will offer therapeutic option at early time points after

SCIs. After preclinical success, the uses of hESCs-ODPs are being evaluated into clinical trials on patients with SCIs. The hESCs-ODPs are currently known as ASTOPC1, while previously it was known as GRNOPC1. It was permitted for clinical trials by US FDA in 2009; however, the proper trials begin in 2010 after being evaluated for safety reason in patients as it developed cysts in animal models [42, 43]. While for some unknown reasons Geron-Corporation ceases the trials, another corporation Asterias Biotherapeutics begin the same trials in phase 1 (NCT01217008) on individuals suffering from subacute thoracic SCIs. The trial was concluded in year 2013 with positive results where safety and tolerability was achieved with no serious fallouts [44, 45]. A year after, Asterias Biotherapeutics initiated a new clinical trial of phase I/IIa (NCT02302157) involving the use of hESCs-ODPs for treatments of sensorimotor complete cervical SCIs, which is expected to complete in year 2018 [44]. Since direct transplantation of hESCs poses a risk of forming teratomas and problem of differentiating into exact cells progeny within a body [41], the highly purified ODPs that are freshly derived from hESCs will offer a best treatment option for patients with SCIs.

#### *5.1.2. Fetal brain-derived human central nervous system stem cell/neural precursors*

The skill of isolation, proliferation and genetic manipulation of ESCs is one of the most important accomplishments in experimental stem cells biology [46]. An isolation of ESCs and their controlled proliferation into neural precursors population has been achieved in variety of preclinical models. After transplantation of ESC-derived neural precursors into the CNS of animal models, the cells have been observed to assimilate well into the recipient tissue and have also shown to improve locomotional recovery in injured rat spinal cord [46, 47]. To evaluate *in vivo* differentiation of hESC-derived neural precursors, a study has shown that these cells were able to integrate, migrate and differentiate into a host tissue [40]. After the preclinical validations and successful outcomes from ESC-derived neural precursors, they are being evaluated in clinical trials with a name HuCNS-SC. The HuCNS-SCs are highly purified fetal brain-derived human CNS stem cells, which have been shown to promote neuroprotection after SCIs [48]. In addition to its use for SCIs, HuCNS-SCs have been used in clinical trials for other disorders including neuronal ceroid lipofuscinosis, age-related macular degeneration and Pelizaeus-Merzbacher disease [48–51]. Following transplantation, HuCNS-SCs are shown to differentiate into neurons and glia and also retained semipermanent survival ability in host tissues. They have been recently evaluated in phase I/II clinical trials (NCT01321333) for safety and preliminary efficacy in patients with subacute SCI via intramedullary transplantation into thoracic spinal cord region [44]. In the clinical outcome from this trial (NCT01321333) that involved 5-year follow-up period, absolutely no safety issues have been documented [52].

#### *5.1.3. Umbilical cord blood-derived mononuclear cells*

Transplantation of human umbilical cord blood-derived stem cells has been reported to migrate well and promote therapeutic recovery from neurological injuries such as stroke and SCIs [53]. Following intravenous administration of human umbilical cord blood-derived stem cells, a study has demonstrated that the transplanted cells were able to improve behavioral properties of induced SCI [53]. Another preclinical study has reported functional locomotory effect following the administration of human umbilical cord blood cells in combination with

brain-derived neutrophic factor into the SCI rat model [54]. In addition to preclinical studies on animal models, a case study on human (37-year-old female) patient with SCI has reported an injection of human umbilical cord blood-derived stem cells. In this study, it was shown that cell transplantation ameliorates sensory perception and movement of body parts, based on functional and morphological analysis [55]. Recently, the transplantation of umbilical cord blood-derived mononuclear cells (UCBMC) has been tested in phase I/II clinical trials (NCT01354483; NCT01471613) for treatment of acute, subacute and chronic SCIs in combination with neuroprotective agents such as lithium carbonate and methylprednisolone [44]. Following transplantation, these cells have been observed to decrease sensimotor injury and other associated cerebral deficiency [56]. In one of the clinical trial outcomes involving UCBMC (NCT01354483), the cellular transplantation was observed to be safe while some recipients were appeared to regain sensorimotor function [57].

#### *5.1.4. Human ES-derived motor neurons*

It has been reported that growth signaling pathway-related factors are able to prompt mouse ESCs differentiation into vertebral progenitor cells, followed by subsequent differentiation into motor neurons [58]. These ESC-derived motor neurons have been recognized with a potential to occupy the embryonic medulla spinalis, lengthen axons and develop synaptic connections with respective muscle tissues [58]. Another study has reported that earlier neuroectodermal cells derived from hESCs population, which expressed *Pax6* but not *Sox1,* were able to differentiate into spinal motor neurons in the presence of retinoic acid and sonic hedgehog. Whereas the neuroectodermal cells in later stages that were expressing both *Pax6* and *Sox1* were unable to differentiate into spinal motor neurons [59]. Following transplantation, these motoneurons have the ability to quickly engraft, maintain proper phenotype and project axonal elongation into peripheral regions in recipient's tissues [60]. These evidences of *in vivo* subsistence of hESC-derived motoneurons are a major way forward to treat SCIs via cellular therapy using motoneurons' transplantation.

### 5.2. Mesenchymal stem cells

The lineage of mesenchymal stem cells (MSCs) is characterized with self-renewal capacity and multipotent stem cells-like abilities. They were originally isolated from the bone marrow [61, 62] and have been reported to differentiate into several cell types [63–68]. The MSCs have also been shown to transdifferentiate into variety of neuronal cells in different animal models [69–72]. The MSCs that qualify transplantational procedure are known as multipotent mesenchymal stromal cells [73], which are having several subtypes that are being therapeutically evaluated for SCIs in different clinical trials. After their transplantation into lesion site, they are thought to be regulated by secretion of trophic factor, which stimulates new vessels formation and anti-inflammatory factors [74]. Moreover, MSCs are being reported to secrete different cytokines and associated growth promoting factors that exhibit both paracrine and autocrine characteristics. These biologically active secreted factors have been shown to suppress the intrinsic immunological repsonse, prevent apoptosis and formation of glial scars, improve angiogenesis and stimulate cell cycle to enhance regenerative activities [75].

*5.2.1. Autologous bone marrow-derived mesenchymal stroma cells*

The autologous bone marrow-derived mesenchymal stromal cells (ABM-MSCs) have been reported *in vivo* to treat different disorders like fistulising Crohn's disease, refractory luminal Crohn's disease and chronic paraplegic SCI [76–78]. In addition to other rodent models, transplantation of ABM-MSCs has shown locomotional recovery in adult mini-pigs models after the induction of SCI [78]. After preclinical evaluation, these ABM-MSCs have been reported to make their way into phase I/II clinical trials for treatment of chronic SCIs [1, 74].

Till date, a couple of the completed clinical trials that involve ABM-MSC transplantation have provided clinical outcomes. In one of the most recent clinical trial (NCT02482194 completed in March 2016) involving ABM-MSCs to treat subacute and chronic SCIs, the transplantation procedure has been documented as safe and doable. This also reported improved sensorimotor functions as well as revealed bladder and bowel improvement [79]. The phase 1 clinical trial (NCT01325103), which has been completed in December 2012 involved ABM-MSC transplantation in patients with chronic traumatic SCIs, has reported that direct cellular transplantation into lesion site is safe, viable and may encourage sensorimotor functions. In this trail, eight patients improved lower limbs motor function, mainly in the flexor muscles of hip, while seven patients advanced American Spinal Injury Association Impairment Scale (AIS) grades to B or C and nine patients improved urological functions [80]. Another phase 1/2 clinical trial that has been completed in October 2010 involving patients of subacute thoracic SCIs has reported that following ABM-MSC transplantation, noticeable recovery was observed in five patients (45.5%). ASIA sensorimotor score increased and patients were able to walk using a support [81].

In addition to the clinical trials mentioned above, there are several ongoing clinical trials from phase 1/2 to 2/3 that involve the use of ABM-MSC transplantation in patients with chronic cervical, thoracic and lumbar SCIs. These clinical trials (NCT02574585; NCT01676441; NCT02570932; NCT01730183; NCT01446640; NCT02687672; NCT02981576; NCT02260713; NCT02923817; NCT02574572; NCT02009124) are expected to be completed in the upcoming years, and the clinical outcomes from these trials are still pending as mentioned in **Table 1**.

*5.2.2. Umbilical cord-derived MSCs*

Since the clinical use of ABM-MSCs might be unfavorable due to the practice of vastly invasive method, as well as the ratio of BM-MSCs decreases while differentiation increases with passage of age, the utilization of umbilical cord blood-derived MSCs is a best substitute for BM-MSCs [82]. It has been reported that umbilical cord blood-derived MSCs can be grown for longer time period and are having maximum proliferation potential. In contrast, BM-MSCs require less time to grow and possess low proliferation capacity [82]. A study has reported the transplantation of human umbilical cord-derived MSCs into animal SCI model, which has shown that these cells were able to migrate well into the lesion site and were positive to anti-nuclei antibody (clone 235-10) MAB1281 [83]. Following their preclinical validation, the umbilical cord-derived MSCs have reached to phase I/II clinical trials for the treatment of chronic and/or acute SCIs [1]. One of the most recent clinical trial that involves umbilical cord

| Source | Type of therapeutic cells | Combination therapy | Type of spinal cord injury | Clinical phase reached | Year of completion | Outcome | Clinical trials identifiers/ References |
|---|---|---|---|---|---|---|---|
| Embryo-derived cell population | GRNOPC1 (hESCs-ODPs) | _ | Complete, subacute SCI | Phase 1 | Jul-2013 | Safety and tolerability were achieved with no serious fallouts | NCT01217008 [45] |
| | AST-OPC1 | _ | Subacute cervical SCIs | Phase 1/ 2a | Dec-2018 | Pending | NCT02302157 |
| | HuCNS-SC | _ | Thoracic chronic SCIs | Phase 1/ 2 | Apr-2015 | After 5 years of clinical follow-up, absolutely no safety issues have been documented | NCT01321333 [52] |
| | UCBMC | Methylprednisolone and lithium carbonate | Chronic SCIs | Phase 1/ 2 | Dec-2013 | UCBMC' transplantation was observed to be safe while some recipients were appeared to regain sensorimotor function | NCT01354483 [57] |
| | UCBMC | Lithium carbonate | Acute and subacute SCI | Phase 1/ 2 | Jan-2014 | No study results posted | NCT01471613 |
| Mesenchymal stem cells | ABM-MSCs | _ | Subacute and chronic SCI | Phase 1 | Mar-2016 | Transplantation appeared to be safe and viable, resulted in improved sensorimotor functions and also revealed bladder and bowel improvement | NCT02482194 [79] |
| | Autologous bone marrow MSC | _ | Chronic traumatic SCI | Phase 1 | Dec-2012 | Intralesional transplantation of ABM-MSCs is safe, feasible and may promote neurological improvements | NCT01325103 [80] |
| | ABM-MSCs | _ | Subacute thoracic SCI | Phase 1/ 2 | Oct-2010 | Noticeable recovery was observed in five patients (45.5%). ASIA sensorimotor score increased and patients were able to walk using a support | [81] |
| | AMB-MSCs | _ | Thoracic and lumbar chronic and complete SCI | Phase 2 | Dec-2017 | Pending | NCT02574585 |
| | ABM-MSCs | _ | Cervical SCI | Phase 2/ 3 | Dec-2020 | Pending | NCT01676441 |

| Source | Type of therapeutic cells | Combination therapy | Type of spinal cord injury | Clinical phase reached | Year of completion | Outcome | Clinical trials identifiers/ References |
|---|---|---|---|---|---|---|---|
| | ABM-MSCs | _ | Chronic SCI | Phase 2 | Feb-2018 | Pending | NCT02570932 |
| | ABM-MSCs | _ | Cervical, thoracic and lumbar SCIs | Phase 1/ 2 | 11 Jan-2014 | Pending | NCT01730183 |
| | ABM-MSCs | _ | Thoracic and lumbar SCIs | Phase 1/ 2 | Jun-2014 | Pending | NCT01446640 |
| | ABM or Leukapheresis-derived MSCs | _ | Chronic traumatic SCI | Phase 1/ 2 | Dec-2021 | Pending | NCT02687672; NCT02981576 |
| | ABM-MSCs | _ | Acute SCI | Phase 1/ 2 | Nov-2017 | Pending | NCT02260713 |
| | ABM-derived mononuclear cells | _ | SCIs | Phase 2 | Jun-2019 | Pending | NCT02923817 |
| | ABM-MSCs | _ | Cervical chronic and complete SCI | Phase 1 | Dec-2016 | No study results posted | NCT02574572 |
| | Autologous bone marrow mononuclear cell | _ | SCIs | Phase 2 | Dec-2016 | No study results posted | NCT02009124 |
| | Umbilical cord Wharton's jelly-derived MSCs | Placebo/XCEL-UMC-BETA | Chronic traumatic thoracic SCIs | Phase 1/ 2a | Apr-2020 | Pending | NCT03003364 |
| | Human umbilical cord-derived MSCs (allogeneic) | Bone marrow mononuclear cells (BMMC) | SCIs | Phase 1/ 2 | Oct-2019 | Trial withdrawn prior to enrollment | NCT02237547 |
| | Umbilical cord-derived MSCs | _ | Complete or incomplete cervical and thoracic SCIs | Phase 1/ 2 | Dec-2018 | Pending | NCT02481440 |
| | Human autologous adipose tissue-derived MSC (hAdMSC) | _ | SCIs | Phase 1 | Feb-2010 | Following cellular transplantation in SCI patients, no safety issues were seen and also the transplanted cells did not develop teratomas | NCT01274975 [85] |
| | N-Ad-MSC (autologous adipose tissue-derived | Hematopoietic stem cells | Traumatic lumbar SCIs | Phase 1 | Oct-2012 | | [86] |

| Source | Type of therapeutic cells | Combination therapy | Type of spinal cord injury | Clinical phase reached | Year of completion | Outcome | Clinical trials identifiers/ References |
|---|---|---|---|---|---|---|---|
| | MSCs differentiated neuronal cells) | | | | | Coadministration of N-Ad-MSC and hematopoietic in patients' CSF is safe and feasible treatment option for SCIs | |
| | Autologous adipose-derived stem cells | _ | Acute SCIs | Phase 1/ 2 | 3 Jan-2015 | Pending | NCT02034669 |
| | Spinal cord-derived neural stem cells | _ | Chronic cervical and thoracic SCIs | Phase 1 | Dec-2022 | Pending | NCT01772810 |
| | MSC-autologous neural stem cells | RMx Biomatrix | Acute, sub-chronic and chronic lumbar and thoracic SCIs | Phase 1/ 2 | Dec-2018 | Pending | NCT02326662 |
| | MSC-derived neural stem cells | NeuroRegen scaffold | Cervical and thoracic SCIs | Phase 1/ 2 | Jun-2018 | Pending | NCT02688049 |
| Peripheral myelinating cells | Autologous human Schwann cells (ahSC) | _ | Subacute lumbar SCIs | Phase 1 | Aug-2016 | Following 1-year assessment, no signs were observed for serious side effects that could be specifically associated to the nerve harvest, cellular transplantation protocol or to the transplanted cells in lesion site | NCT01739023 [91] |
| | Autologous human Schwann cells (ahSC) | Rehabilitation | Chronic lumbar and thoracic SCIs | Phase 1 | Jan-2018 | Pending | NCT02354625 |
| | Autologous olfactory ensheathing glia and olfactory fibroblasts | _ | Subacute or chronic SCIs | Phase 1 | N/A | Pending | NCT01231893 |

**Table 1.** Results of clinical trials of stem cell-based therapy for spinal cord injury.

Wharton's Jelly expanded MSCs with Placebo/XCEL-UMC-BETA intervention is being evaluated against thoracic SCIs in phase 1/2a, which is expected to be completed in April, 2020 (NCT03003364). Another phase 1/2 clinical trial that was testing the use of UC-MSCs in combination with bone marrow mononuclear cells was expected to complete in October 2019; however, it was withdrawn prior to enrolment (NCT02237547). One of the ongoing phase 1/2 clinical trial that purely involves the use of allogenic UC-MSCs is evaluating its safety and viability using intrathecal injections. This trial involves patients with complete or incomplete cervical and thoracic SCIs, which is expected to be completed in December 2018 (NCT02481440).

#### *5.2.3. Autologous adipose-derived MSCs*

In comparison to the umbilical cord blood, another source that has been reported to hold more number of MSCs is adipose tissue. It had been shown that 100% of MSCs can be isolated from adipose tissues compare to 63% of isolation from umbilical cord blood [82]. Since the adipose-derived MSCs have been recognized by immunosuppressant characteristics and less immunogenic behavior, they have been considered as a potential source of treatment for SCIs [84]. A study has reported that after an intravenous administration of human adipose-derived MSCs in murine models (Balb/c-nu nude mice) and humans (n = 8) clinical trial (NCT01274975) for SCIs, no safety issues were seen and also the transplanted cells did not develop teratomas [85]. The use of adipose-derived MSCs has been evaluated in phase I and I/II clinical trials for treatment of different SCIs [1, 44]. A phase 1 clinical trial that has been completed in October 2012 reported that co-administration of autologous adipose-derived MSCs' differentiated neuronal cells (N-Ad-MSC) and hematopoietic in patients' CSF is safe and feasible treatment option for SCIs [86]. Another phase 1/2 clinical trial has evaluated adipose-derived MSCs in patients with acute SCIs, which was expected to be completed in 2015; however, the clinical outcomes are still pending (NCT02034669).

#### *5.2.4. MSC-derived neural stem cells*

A specific cell progeny can be derived from MSCs, which has been tested in different clinical trials that mainly involve MSC-derived neural stem cell (NSC) population. In one of the most recent phase 1 clinical trials, human spinal cord-derived neural stem cells population has been used for transplantation to treat patients with chronic cervical and thoracic SCIs. The clinical outcome form this trial is still pending as the trial is expected to be completed in December 2022 (NCT01772810). A phase 1/2 clinical trial is currently evaluating MSCs-autologous NSC transplantation together with RMx Biomatrix (3D biomatrix) as scaffold for treatment of acute, sub-chronic and chronic lumbar and thoracic SCIs, which is expected to be completed in December 2018 (NCT02326662). Another phase 1/2 clinical trial that is currently ongoing for treatment of patients with cervical and throracic SCIs is utilizing the transplantation of MSCs-NSCs in combination with "NeuroRegen" scaffolds. This trial is expected to be completed in June 2018 (NCT02688049).

### 5.3. Peripheral myelinating cells

In addition to other type of cells, the most relevant cell types for treatment of SCIs are the peripheral myelinating cells, which are mainly damaged during primary and secondary injury

process. Such types of peripheral myelinating cells that have shown promising results in preclinical trials for SCIs and are currently being evaluated in clinical trials include the following.

#### *5.3.1. Autologous human Schwann cells*

Schwann cells have been reported to display significant flexibility in performing a wide range of functions in nervous system through major involvement in ensheating and myelination of axons. Schwann cells are playing crucial regenerative role in supporting regeneration of axons in the PNS, which indicates that the uses of Schwann cell transplantation and autografting will offer regenerative role in damaged CNS [87]. Different studies have reported the differentiation of adult precursor cells into Schwann cells, including a study where precursor cells isolated from skin were able to produce myelinating Schwann cells. Upon transplantation, these Schwann cells were able to improve remyelination and supported locomotional recovery from contusion SCI [88]. Following transplantation, the Schwann cells are characterized by remyelination of damaged axons and maintaining an environment favorable for axonal regrowth by secreting important growth and trophic factors [89]. One of a renowned study has shown that a combination of Schwann cell transplantation and regulation of cyclic adenosine monophosphate (cAMP) levels by using rolipram and/or a cAMP analog (db-cAMP), might improve the overall regenerative roles of Schwann cells in treatment of SCIs [90].

In clinical trials, the autologous human Schwann cells have been evaluated in phase I trials (NCT01739023; NCT02354625) for chronic and subacute SCIs [44]. In one of the most recently completed phase 1 clinical trial, transplantation of autologous human Schwann cells (ahSC) has been evaluated in patients with subacute lumbar SCIs (NCT01739023). In the clinical outcome following 1-year assessment, no signs were observed for serious side effects that could be specifically associated to the nerve harvest, cellular transplantation protocol, or to the transplanted cells in lesion site [91]. Another phase 1 clinical trial that is utilizing ahSCs in combination with rehabilitation to treat chronic lumbar and thoracic SCIs is expected to be completed in January 2018 (NCT02354625).

#### *5.3.2. Autologous olfactory ensheathing glia and olfactory fibroblasts*

The olfactory ensheathing glial cells are belong to a class of macroglia, which are involved in ensheathing demyelinated axons of olfactory neurons. In olfactory bulb, typical and transected olfactory axonal structures are able to move in, regenerate and restore damaged synaptic communications with their respective targets [92]. Moreover, transplantation of olfactory ensheathing glial cells has been reported to improve axonal remyelination within a damaged nervous system [92]. A preclinical study has reported a transplantation of adult rat's olfactory bulb-derived ensheathing glia cells in a SCI's site, where the cells filled the lesion gap through regeneration [93]. In addition to the preclinical success of olfactory ensheathing cell transplantation, a study has reported the feasibility of transplantation of autologous olfactory ensheathing cells into three spinal cord injured patients where the cells were found safe without any serious complication for up to 12 months after transplantation [94]. A subsequent study has reported that transplantation of olfactory ensheathing cells is viable and safe for promoting motor and sensory activities [95]. Therapeutically, the olfactory ensheathing cells

are most likely to maintain their effects via secretion of specific growth promoting factors that develop new olfactory axons and promote axonal regeneration following SCI [96]. At present, the olfactory ensheathing glial and fibroblastic cells are being evaluated in phase I clinical trial (NCT01231893) for treatment of complete SCIs [44].

### 5.4. Induced pluripotent stem cells (iPSCs)

Pluripotency, a special ability of a pluripotent cell to differentiate into any type of body cell, was shown to be induced in adult differentiated cells via the activity of only four embryonic transcription factors—Oct3/4, Sox2, Klf4 and c-Myc. These induced adult cells gaining the ability of pluripotency were termed as "induced pluripotent stem cells" (iPSCs) [97]. This discovery offered a very forthright procedure of how to induce pluripotency in mature cells in a basic laboratory setup, yet the scope of this cell-rewinding discovery was extraordinarily vast in biomedical sciences and regenerative medicine, which earned the principle investigator, Yamanaka, a Nobel Prize in year 2012 [98].

#### *5.4.1. Reprogramming factors*

The reprogramming factors, also known as pluripotency markers, are the main regulators of inducing pluripotency in mature cells via a process of activating pluripotent genes expression. The induction of pluripotency can be achieved via expression of only four reprogramming factors, i.e. OCT3/4, SOX2, KLF4 and c-Myc [99]. POU class 5 homeobox 1 (POU5F1 or OCT4) is being reported to play a significant role in developing embryo and maintaining pluripotent status. It has been observed to bind an octamer motif (ATGCAAAT) of DNA, where it is involved in regulation of several genes that play important part in pluripotency. Oct4 has been observed to frequently regulate in association with Sox2 [100–102]. SRY (sex determining region Y)-box 2 (SOX2) is a transcription factor encoded by *SOX2* intronless gene. It plays an important role to regulate embryonic development and determine cell fate and is usually expressed in developing embryo and neuronal cells [100]. It has been reported that expression of SOX2 is fundamental for maintaining pluripotent status of evolving embryos, whereas its downregulation is associated with mesodermal and endodermal differentiation. Embryos with no expression of SOX2 were found unable to grow and proliferate after implantation [102, 103]. Kruppel-like factor 4 (KLF4 or EZF), a zinc finger protein is a transcription factor that is involved in regular growth of the barrier properties of body skin [100]. KLF4 has been reported to have a higher expression in non-dividing cells and is associated with induction of cell cycle arrest [104, 105]. KLF4 has been shown to specifically regulate genetic stability [106, 107] and promote cellular growth and survival [108]; however, in some cases, KLF4 has been reported to induce cell death [109, 110]. c-Myc, a nuclear phosphoprotein, has been recognized to play multiple functions, including cell cycle multiplication, programmed cell death and cellular propagation, via transcriptional regulation of particular genes [100]. The efficacy of OCT3/4, SOX2 and KLF4 is shown to be enhanced by the expression of an enhancer factor c-Myc [111].

#### *5.4.2. Mechanisms of cellular reprogramming*

In mechanism of cellular reprogramming, three pluripotency markers (OCT3/4, SOX2 and KLF4) have been observed to greatly influence multiple genes expression in iPSCs [112]. In

iPSCs, the augmented factors binding at promoter regions are linked with elevated level of transcription, signifying the fact that OCT3/4, SOX2 and KLF4 are involved in genes regulation predominantly as activators of transcription [113].

For induction of cellular reprogramming in adult cells, four strategies can be employed that include nuclear transfer, fusion of cells, cellular explantation and infection through retroviral vectors [114]. In the mechanism of nuclear transfer, direct administration of a viable donor somatic nucleus into an enucleated egg cell, followed by implantation in a surrogate mother, can develop a reproductive clone. If the enucleated egg cell with implanted somatic nucleus is grown *in vitro*, it can generate inherently matched ESCs population. In mechanism of cell fusion, culture of adult body cells with ESCs can give rise to hybrid progeny of cells that can entirely exhibit pluripotency. In another strategy of cellular explantation, adult body cell cultures can be directly induced to gain pluripotency via reprogramming factors. In fourth strategy of cellular reprogramming, infection through retroviral vectors carrying distinct factors can induce reprogramming to generate iPSCs [114].

### *5.4.3. Trials involving iPSCs for SCIs*

A preclinical study has reported that following transplantation of human iPSC-derived neurospheres into spinal cord-injured mice model, a locomotional recovery from SCI was achieved, signifying the importance of human iPSC-derived neurospheres in regenerative medicines [115]. Another study has reported the transplantation of human iPSC-derived neural stem cells into monkeys' specie that promoted locomotory function after SCI, without inducing teratomas [116]. One of a report has stated that iPSCs have the ability to generate three important functional cell types of the CNS, i.e. astrocytes, oligodendrocytes and neurons [117]. An optimization of efficient protocols that can be utilized to generate constant and long-term population of neural stem cells from ESCs and iPSCs has been demonstrated [118, 119]. These types of cells have displayed stable features, for example constant expanding properties, consistent differentiation into neurons and glia and the ability of producing efficient established neurons *in vitro*. Another study has reported that following transplantation of such long-term stemness-rich cells (iPSC-derived neural stem cells) into SCI mice model, improved remyelination and axonal regrowth were observed with additional support for subsistence of endogenic neurons [120].

In one of an important study, cells from a healthy man of 86 years of age were induced to generate iPSCs, from which neural stem cells were generated and transplanted into rats exhibiting immunodeficiency following SCI. After 12 weeks of C5 lateral hemi-sections, iPSCs endured and generated neuronal and glial cells, extending large number of axons from injured area to almost the complete distance of rat CNS that subsequently developed synaptic communications with host neurons [121]. Another study on human iPSC-derived neural progenitors known as IMR90 has reported functional recovery after IMR90 transplantation in SCI rat models. It was shown that iPSCs have the ability to generate functional neurons, which resulted in long-term functional recovery from SCI [122]. Altogether, several studies have reported that following transplantation of iPSC-derived neural stem/precursor cells, locomotory function was improved/recovered in spinal cord-injured animal models [115, 116, 120, 123, 124]. In contrast, other studies have reported that transplantation of clones containing

human iPSC-derived neural stem/precursor cells, e.g. clone-253G1 and 836B3, has been reported to induce teratomas and suppress locomotory function after long-term follow-up. In addition, the induced teratomas were made up of undifferentiated Nestin-positive cells of human origin [125, 126]. For this purpose, one of a recent study is paving the ways to tackle such problems of teratoma formation and locomotory inhibition. In this study, it was shown that human iPSC-derived neural stem/precursor cells that were pre-treated with γ-secretase inhibitor (GSI) induce differentiation and development of neuronal cells, whereas it also recovers host neural circuitry. Moreover, the incredible results showed that following transplantation of these cells with GSI pre-treatment after SCI, tumorigenesis was prevented and locomotory function was maintained [126].

## 6. Safety concerns regarding the use of cell transplantation

Therapeutic approaches of cellular transplantation are revolutionizing the field of regenerative medicine; however, it also raises different safety concerns regarding several associated risk factors including tumorigenesis, adverse immunogenic response, transmission of extrinsic factors and differentiation into unwanted cellular progeny [127, 128].

### 6.1. Cyst/tumor formation

The intrinsic characteristics of ESCs and adult stem cells (ASCs) correlate to cancerous cells, for instance, their extended lifespan, comparative apoptotic resistance and potential to divide for longer time period [129]. Moreover, maintenance of required growth signals and other tightly regulated mechanisms can be observed in both cancerous and stem cells [130, 131]. Thus, the pluripotency of ESCs and multipotency of adult stem cells are regarded as the crucial aspect of developing tumors. The tumorigenic potential of cellular transplantation therapy could be intrinsic or adventitious, depending upon the microenvironment of transplanted cells [130]. It has been reported that following differentiation of stem cells into mature cells, the later can induce tumorigenesis due to acquiring several mutations in the process of parent-stem cells culture [132].

### 6.2. Immune rejection

An immune rejection is another apparent safety concern that could escalate after cellular transplantation therapy. A transplanted cell could either directly prompt an immunogenic reaction or could have a regulatory influence on the immune system [133]. Several factors may impact the host-induced immunogenicity depending upon the location of cellular transplantation and number of administered doses [134]. MSCs and other ESC-derived progeny are being described as immunoprivileged and hold little immunogenicity [135]. It has been shown that MSCs can cause suppression of T cell to proliferate, prevent monocytes to differentiate [136] and can also hinder B cell to proliferate and/or differentiate [137]. In addition, extracts from both mouse and hESCs have been shown to maintain immune regulatory characteristics of ESCs [138].

### 6.3. Other physiological side effects

One of a recent study has reported that a male dominant hormone testosterone has the ability to stimulate proliferation of human adult MSCs and endothelial precursor cells, while preserving their stemness properties [139]. Transplantation of these cells in a hyper testosterones secreting recipient will raise several safety concerns.

## 7. Techniques for "*in-vivo* tracking" of transplanted cells

One of the most essential and obvious steps to follow after cellular transplantation is to track down the implanted cells in host tissues. To date, several studies have reported the use of *in vivo* tracking system where an investigator can observe and analyze transplanted cells to evaluate their extensive status including site of cell transplantation, cellular migration, proliferation, differentiation into desired cell types, long-term self-renewal and their integration within a host tissue [140]. Using MRI technique where a superparamagnetic iron oxide works as a contrast mediator, transplanted cells can be tracked down *in vivo* [141]. One of a study has shown that using 3D microtopographic scaffolds, reprogrammed neuronal cells were capable of colonizing damaged neural cells to replace with transplantable cells [142]. It has been reported that transplanted MSCs, labeled with established gadolinium-based MRI contrast agent, i.e. Gadoteridol, were effectively traced via *in vivo* tracking in a SCI mouse model. A procedure that was employed during the *in vivo* tracking was established on hypo-osmotic shock that induced an osmolality-contingent permeabilization and physical alterations in cellular membrane [143]. Hence the *in vivo* cell tracking techniques are evolving; further development in these technologies will help to optimize future cellular transplantation therapy protocols for SCIs.

## 8. Success story and controversies of cell transplantation in patients with SCIs

Researchers in the field of cellular therapy and regenerative medicines are restraining to directly inject hESCs or iPSCs in humans, but rather more inclined to evaluate hESCs- or human iPSC-derived cell population, i.e. ODPs, HuCNS-SC, Schwann cells, olfactory ensheathing cells, umbilical cord blood mononuclear cells, autologous BMSCs and umbilical cord blood- and adipose-derived MSCs, as evident from the recent and ongoing clinical trials —**Table 1**. In contrast to direct transplantation of ESCs or iPSCs, direct administration of the above-mentioned derived cells is only limited to form single-specific cell progeny and also possesses lower risk of developing teratomas in host specie [144].

Till date, success has been made in cellular transplantation therapies for SCIs as their usages and procedures have now reached to clinical trials; however, these procedures are still at their early stages with no further than phase I or phase I/II clinical trials [5]. Nevertheless, all the

preclinical and clinical studies have improved our understanding of repair mechanism following cellular transplantations. As mentioned earlier, novel methods are emerging to tackle all the associated risks with cellular transplantation, where tumorigenesis can be prevented by using specialized protocols [126]. Up till now, even after reaching into clinical trials, fundamental associations between locomotory functional development and specific mechanisms in SCIs have rarely been achieved [145]. Yet, some studies have reported clinical success by using cellular transplantation therapies for SCIs. One of such study has been conducted in 2003, where a clinician directly transplanted OECs derived from aborted fetuses in Chinese hospital. In this contentious experiment, 171 spinal cord-injured patients were reported to have recovered from SCIs without any associated risk [146, 147]. Two years later, a Korean research division claimed that umbilical cord blood-derived MSCs have the ability to recover locomotory function in a patient who was suffering from a complete disability for several years [55]. The claims made in these studies received controversial responses because they were associated with ethical challenges, greater risk association and still require appropriate and accurate clinical confirmations [147]. Nonetheless, cellular transplantation therapies for SCIs are becoming more exciting and interesting, especially when research studies of lower immune rejections and preventing teratoma formation are paving the ways for future regenerative research [126, 148].

## 9. Future prospects

In the current era of regenerative medicine, cell-based transplantation therapies have advanced our approaches to an extent that these therapies soon will be capable of treating subacute and chronic SCIs in the very near future. The ongoing improvements and assessments of associated risks with cellular transplantation, improved relevance of preclinical models, long-term enhanced recovery, *in vivo* tracking of transplanted cells and preventing teratoma formations are advancing the future aspects of these therapies for SCIs [5, 126, 145]. Cells that are derived from hESCs and iPSCs are showing promising results in preclinical and clinical trials, indicating their dominance in the prospective field of personalized and regenerative medicines. In particular, the iPSC-derived cell progeny that is disease and patient-specific, is evidently the best option as it carries lower immune rejection and is limited to particular cell types [149]. In addition to the ongoing comprehensive neuroregenerative and neuroprotective therapeutic strategies for SCIs [5], newer technologies are evolving including neuroscience-based computational and robotic rehabilitational therapies. In 2014, a group of Swiss scientists reported an innovative discovery for treatment of complete SCI using neuroscience modulation-based therapeutic approach to control spinal sensorimotor network, without involving cellular transplantation techniques. In this study, an electric stimulus-based procedure was used to assist a non-standing paralytic rat model with complete injured spinal cord to move the paralyzed feet again and even climbed staircases [150]. The neurorobotic techniques-based therapies for SCIs are also emerging, as recently being reported where a volunteer-driven exoskeleton was used as an innovative robotic device for rehabilitation in chronic SCIs [151]. These exoskeleton

robotic devices work as a wearable outfit that regulates the external movements by detecting internal nerve signals in patients with SCIs. However, such neuroscience-based computational and robotic rehabilitation therapies are evolving for treatment of SCIs, yet they are in the initial phases of development and do not offer a complete cure to fully repair and regenerate injured spinal cord. Nevertheless, any sort of therapeutic strategy that can rehabilitate and improve functional recovery will always be considered a therapy-of-future for SCIs, as being phrased "something is better than nothing." In a nutshell, the only therapeutic approach that could be able to completely cure SCIs in near future is the use of cell-based transplantation strategies.

## 10. Conclusion

Spinal cord injury, a devastating condition where patient feels sharpest pain shooting from vertebrae through the neck up head and subsequent paralysis has unfortunately no proper treatment. In recent times across the globe, a renewed attention has been diverted to find and develop a complete treatment for SCIs. In addition to neuroregenerative, neuroprotective and neuro-computational strategies, cellular transplantations are considered the most relevant, inspiring and encouraging therapies for treatment of SCIs. To date, numerous preclinical and clinical studies have confirmed cellular regeneration and locomotory functional recovery from SCIs following cellular transplantation. Instead of direct transplantation of hESCs and iPSCs, their derived cell population is the most preferred type of cells for successful transplantational recovery, as evident from their extents into the clinical trials. Novel approaches have revealed to specifically generate desired cell type, track the transplanted cells *in vivo* and prevent associated risks of tumorigenesis and loss of locomotional functions. Accomplishments from these newer improved strategies are opening new avenues for future research to completely cure SCIs.

## Acknowledgements

We are thankful to the Deanship of Scientific Research, King Abdulaziz University (DSR) and King Abdulaziz Center for Science and Technology (KACST), Saudi Arabia, for their technical and financial support in our various research projects. We would also like to acknowledge "Higher Education Commission" of Pakistan and "IBMS, Khyber Medical University" for their financial support.

## Conflict of interest

The authors declare that there are no conflicts of interest.

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*Edited by Yannis Dionyssiotis*

Spinal cord injury is a severe condition leading to serious neurological dysfunctions and changes a person's life in a sudden way. Understanding the pathophysiology of spinal cord injury will improve the prognosis and reintegration to the society of spinal cord-injured subjects. The book *Essentials of Spinal Cord Injury Medicine* includes seven chapters with valuable information addressing hot topics related to spinal cord injury, ranging from pathophysiology, nontraumatic spinal cord injury, complications to exoskeletons, and research therapies with mesenchymal stem cells. The book could be a valued reference for physiatrists, neurosurgeons, orthopedic surgeons, neurologists and physical therapists.

Published in London, UK


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ISBN 978-1-83881-275-1