Advanced Drug Delivery Reviews 82–83 (2015) 153–159

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Biomarkers of spinal cord injury and ensuing bladder dysfunction ☆

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ARTICLE INFO

Available online 14 November 2014

Keywords:
Spinal cord injury
Regeneration
Structural biomarkers
Inflammatory biomarkers
Neuroimaging
Urinary bladder
Neurogenic detrusor overactivity

ABSTRACT

During the acute phase of SCI, the extension and residual neurological deficits that will persist after the waning of the spinal shock period are difficult to estimate on clinical grounds. Therefore, objective biomarkers able to estimate the extension of the lesion and the degree of neurological recovery are of great importance. Research has been focused on the detection of structural neuronal and glial proteins that leak from damaged cells, inflammatory proteins recruited to remove necrotic debris and more accurate neuroimaging methods that are able to discriminate the extension and functional consequences of the SCI.
Urinary biomarkers are also being investigated to estimate functional changes that typically affect bladder function following SCI which can endanger patient's life in the long run.
Future studies are needed to precisely characterize the composition and function of the glial scar that appears in the area of SCI and repeals axonal growth, therefore preventing axonal rewiring.

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1. Introduction

Spinal cord injury (SCI) is a devastating event that most often affects individuals in their peak productive phase of life. Leading causes include falls, sports-related injuries and motor vehicle crashes, which result in a transection, contusion or ischemic insult [1]. Cervical and high thoracic segments are typically the most affected due to abrupt flexion or rotation of the head, neck or back.

SCI induces cord changes at the injury site in three steps. The initial step refers to direct tissue destruction (compression, laceration, shearing of the cord) that results in profound histological changes at the injured location [2]. The second step refers to a series of negative events that include vascular changes, production of free radicals, lipid peroxidation, altered ATP production, invasion by macrophages, activation of resident glial cells, and neuronal and glial apoptosis, all of which may contribute to further damage of the injured area [1,2]. The final step consists in the formation of a glial scar, composed by neurite outgrowth inhibitory proteins (NOGO), chondroitin sulfate proteoglycans (CSPGs), myelin-associated glycoprotein (MAG), and oligodendrocyte myelin

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Regenerative Medicine Strategies in Urology".

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http://dx.doi.org/10.1016/j.addr.2014.11.007
0169-409X/

glycoprotein (OMgp) [3,4]. This glial scar is highly repulsive to axonal growth, making difficult appropriate rewiring.

Depending on the magnitude of SCI, affected individuals may present complete or incomplete loss of sensory, motor and visceral functions. Patients with incomplete cord sectioning tend to present more recovery of limb function than those with complete transections [5]. Some neurological problems may be overcome, at least partially, during the first year after SCI [6].

Currently, the prognosis of SCI patients is made with a clinical neurologic assessment, which requires patients to demonstrate residual strength in particular muscles and report sensation to pin-prick and light touch throughout the body [7]. This is often very difficult or even impossible to accomplish in early stages if patients suffer from multiple injuries or are under sedation [8]. Many patients will have a period of spinal shock, with a variable duration after SCI during which the activity of spinal cord (SC) below the lesion is very residual. In addition, bladder dysfunction either during the period of spinal shock or after recovery will severely compromise these patients or eventually put in danger their long term survival.

In this context, biomarkers become attractive tools to better characterize SCI patients, predict outcomes and propose the most adequate management. A specific section dealing with biomarkers of bladder dysfunction following SCI is also included in this review. Eventually, biomarkers identified in the context of SCI may also demonstrate some usefulness in the management of other neurological diseases including stroke or multiple sclerosis.

2. Social and economic burden of SCI

The incidence and prevalence of SCI are difficult to estimate on a yearly basis but recent surveys indicate that in the USA alone more than 12 thousand new cases occur per year and approximately 230 to 320 thousand individuals live with chronic SCI [9,10]. The worldwide estimations indicate that 2 million people live with SCI [11]. With the current medical emergency services, surgical procedures, antibiotics, adequate lower urinary tract care and improved rehabilitation policies, life expectancies for persons with SCI have increased substantially and are expected to raise in the future [12–15]. Once considered to be an injury of the very young, the life-style changes and the increasing aged population in many areas of the world has altered the epidemiology of SCI, with the average age at which SCI occurs rising from 29 years in the mid-1970s to 40 years in 2005 [12–16]. In addition life span of SCI patients has increased dramatically along the last decades due to a better management of the multiple organ dysfunctions associated with the SCI. Nevertheless, at any age, a SCI has an enormous impact, not only for the individual on a personal level, but also for the society as a whole in what concerns the costs of the acute and chronic care [12–16]. The estimated economic burden per individual with SCI varies between 1.5 and 3 million dollars, depending on the injury location [17] with a total annual charge attributable to SCI-related hospitalizations of approximately 1.69 billion dollars in the U.S. and around 2.67 billion dollars in Canada [18,19]. It is unclear if the high cost of urinary incontinence related with SCI is already included in those estimates.

3. Biomarkers of SCI

A biomarker is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention", according to the Biomarkers Definitions Working Group, sponsored by the National Institutes of Health [20]. Therefore, biomarkers are considered as important tools to identify the causing agent(s) of a specific pathology, establish the prognosis, develop new drugs, obtain information about the effects of a specific treatment and follow disease progression. A vast array of tests falls within this scope, spanning from biochemical elements present in the serum, cerebrospinal fluid (CSF) or urine and to imaging techniques. An ideal biomarker for lesions of the central nervous system should have the following properties [21]:

- specificity for the central nervous system
- quick release in measurable amounts into the CSF, blood or urine
- easy and ready to detect in samples
- predict the severity and outcome of the injury from an early stage
- to influence the treatment decision
- to be measured by reproducible and reasonably priced methods, and
- minimally influenced by confounding elements.

In the case of SCI, in which the cause is easily identifiable, biomarkers may be important to evaluate the extent of traumatic injury, particularly at an early stage to make a more accurate prediction on how the patient will progress, to follow scar formation and axonal rewiring, and to search for new and more effective treatments.

Whereas much data has been gathered in experimental and clinical studies addressing the role of biomarkers in traumatic brain injury (TBI) [21,22], less has been investigated in the context of SCI. As samples for damaged spinal tissue cannot be obtained from affected individuals, CSF and serum have received considerable attention as sources of biomarkers. In addition, neuroimaging and agents able to modulate axonal growth namely neurotrophins have also been object of research.

3.1. Structural biomarkers

These biomarkers are released by cells located at the injury site and accumulate in the CSF. If the blood–brain-barrier (BBB) is compromised, some biomarkers will be released in the circulation and may be detected in the serum. Examples of such biomarkers include cytoskeletal proteins of neurones and glial cells and cellular metabolites.

Tau is a microtubule associated protein present in axons, where it participates in anterograde transport [23,24]. It was initially analyzed in the CSF of patients with or without neurologic complication after aortic surgery due to stroke or traumatic brain injury [25]. The concentration of both intact and cleaved forms of *Tau* was higher in the CSF of SCI patients (and also in TBI patients) than in patients without any neurological complications. *Tau* was proposed as a biomarker to separate, at an early time point (6 to 24 h post-surgery), patients with or without complications [25]. A more recent study has measured *Tau* concentration in the CSF of patients with complete and incomplete SCI [26]. CSF samples were collected over a period of 72 h after spinal injury. It was suggested that values determined at 24 h post-injury correlated with the severity of the injury and segmental motor recovery at 6 months, also supporting *Tau* as a biomarker of SCI recovery [26]. These observations were recently validated in a dog model [27]. Furthermore, *Tau* can also be detected in the serum. To our knowledge, it has not been measured in the serum of SCI patients but some investigators have analyzed its levels after TBI. *Tau* levels were very low in serum samples obtained from TBI patients and the authors found a poor correlation with severity and a poor prognostic value for motor or sensory recovery [28]. It should be noticed that the levels of *Tau* in the serum are usually much lower than in the CSF. Thus, the ratio between *Tau* levels in the two fluids may serve as an indicator of the degree of compromise of the BBB [29].

Neurofilaments (NFs) are important components of the axonal cytoskeleton and usually divided according to their molecular weight into light, medium and heavy NFs [30–32]. Their amino acid composition has several repeats of the sequence lysine–serine–proline, of which serine is highly phosphorylated in neuropathologies [33]. The presence of phosphoNFs in the CSF and serum has been studied both in humans and animals. The concentration of NFs was initially measured in the serum of SCI rats (and also TBI) and shown to be more elevated than in intact animals, with a peak detected 2 days after injury [34,35]. Also in rats, the levels of serum phosphoNFs, particularly heavy NFs, have been used to monitor the effect of minocycline treatment for SCI [36].