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Review

The role of timing in the treatment of spinal cord injury

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ABSTRACT

Regeneration failure after primary spinal cord injury (SCI) leads to diverse clinical complications in a severity- and level of SCI-dependent manner. The cost of treating both of them (initial regeneration failure and following complications) would be prohibitive, particularly in less developed nations. The well-recognized circumstances arose from primary SCI include excitotoxicity and inflammation. SCI increases concentrations of extracellular amino acids (EAAs) in the severity-dependent manner and the maximum level of EAAs at the injury site will be reduced by distance from the injury site. Increased concentrations of EAAs and their signaling result in energy and metabolic changes and eventually neurotoxicity. Therefore EAAs play a crucial role in moving towards secondary stage of SCI. There is a close correspondence between severity of SCI and intensity of acute inflammatory response, which includes proinflammatory cytokines (IL-1β, TNF-α, and IL-6) and immune cells (neutrophils, microglia, and mast cells). The communication between microglia and astrocytes mediate formation of astroglial scar. The scar is thought to diminish the spread of inflammation and lesion volume, and on the other side poses an obstacle to achieving axon regeneration. Moreover, mast cells exert an anti-inflammatory role in the ground of injured spinal cord by degradation of proinflammatory mediators, while mast cells-derived histamine may cause excitotoxicity. Therefore research suggests a very double-sword remark about the work of inflammatory mediators in the injured spinal cord. Myelin associated inhibitors (MAIs) are among the growing list of extrinsic inhibitors of neuroregeneration in the injured-CNS. They function via NgR-dependent mechanisms. The time for intervention by NgR antagonists must be fixed according to the expression pattern of this receptor and its dependent MAIs after SCI. Altogether, experimental studies suggest potential benefits of combating EAAs, inflammatory mediators, and MAIs during the first minutes, hours and weeks after SCI, respectively. However, acute inflammation initially induced by SCI tends to be permanent, even at several years after SCI. This supports the notion that paying attention to inflammation must persist through time. The consideration of seconds-dependent state of spinal cord after primary injury is a very therapeutic and also preventive approach against future possible complications. It is thereby possible to propose "timing", which is perfectly practicable throughout the world, as an effective campaign against the final failure of SCI.

Contents

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1. Introduction

The increasing burden of spinal cord injury (SCI) worldwide (Table 1) and ensuing complications explain growing demand for rehabilitation programs and hospital-based services. SCI can cause various serious complications including neurogenic bladder or bowel dysfunction, sexual issues, autonomic hyperreflexia, urinary tract infections, respiratory and gastrointestinal problems, hepatocellular injury, psychological dysfunction, and so forth. Complications associated with SCI can vary significantly dependent on the level of injury. For example, respiratory problems and autonomic dysreflexia frequently occur in cervical SCI. More precisely, Ng et al. reported higher rates of abdominal bloating in patients with cervical (OR = 9.5) and lumbar (OR = 12) SCI compared with thoracic SCI, and as well higher prevalence of constipation in patients with cervical (OR = 5.6) compared with lumbar SCI [3]. The impact of SCI and related complications on the economic snapshot is widely acknowledged so that studies suggest that patients' income and educational level can be used to predict the risk of premature mortality after SCI. As demonstrated in [4], the highest and lowest mortality rates were observed among low-income (less than $25,000/year) and high-income (more than $75,000/year) group, respectively. Moreover, studies have shown that tetraplegics who live in the lower-resourced countries encounter more problems in activity and participation than their counterparts who live in high-resourced countries [5].

There is ample evidence regarding the epidemiology of SCI in the most areas around the world. Further it seems that the extrapolative model can overcome the limitation of inadequate data in the rest of areas (Table 1) [6]. Despite these facts, a therapeutic gap still persists between developed and developing countries. As mentioned above, the level of SCI is the main determinant of related complications. But the level of SCI is an unchangeable factor. In addition to the significance of the level of injury, the current state of knowledge leads to this conclusion that practical interventions for patients with SCI should be initiated as early as possible and particularly in the acute phase. Thus, it is of fundamental importance to prepare a chronological schema for physicians-particularly for those who reside in developing and undeveloped countries-to make a problem-solving approach to the patients with SCI. The present review was designed to draw a piece of this scheme.

2. The pathophysiological phases of SCI

To explore all of the possible avenues to assess the efficacy of therapeutic interventions in patients with SCI, the pathophysiology of SCI is discussed under two main headings: primary injury and

Table 1
Traumatic Spinal Cord Injury (T-SCI) vs. Non-Traumatic Spinal Cord Injury (NT-SCI).

	T-SCI	References	NT-SCI	References
Annual incident rate	15–40 per million (maximum rate: North America → 40/million, and minimum rate: Austria →15/million) Global annual rate: 23/million	[6]	6–76 per million (maximum rate: North America, high income median → 76/million, and minimum rate: western Europe median → 6/million)	[90]
Prevalence	Global: 236–4187/million (North America, high income: 721–4187/million, Asia south and SouthEast: 236–464/million, Australasia: 370–681/million, and Western Europe: 280–316/million)	[6]	India: 2310/million Canada: 1120/million	[90]
Leading causes	1)Land transport: North America, Central Europe, West Africa, North Africa, southern Africa, Australasia 2)Falls: eastern Europe, south Asia, Oceania 3)Land transport and falls: East Asia, pacific Asia (high income), southeast Asia, Western Europe, Latin America	[6]	1)Degenerative conditions and tumors: developed countries 2)Infections (particularly tuberculosis and HIV): developing countries	[90]
Age of patients	Mean: 46.3 (Austria) Mean: 40.2 (a retrospective study of 441 patients with SCI admitted to the clinic for rehabilitation Dr M. Zotovic, Belgrade, Serbia from January 2000 to December 2009)	[91] [92]	Mean: 54.5 Mean: 55.5	[91] [92]
Costs for initial admission	Mean: $A53,931	[91]	Mean: $A18,430	[91]
Length of initial admission (days)	Mean: 51.3	[91]	Mean: 16.5	[91]
The mean admission total FIM (functional independence measure) score	77.63 ± 11.31	[92]	86.82 ± 11.38	[92]
The mean discharge total FIM score	101.32 ± 18.12	[92]	109.06 ± 11.27	[92]
Complete lesion	42.2%	[92]	21.6%	[92]
The most common type of injury	Cervical injuries: 40.5% (Thoracic injuries: 38.4% and lumbar injuries: 21.1%)	[92]	Thoracic injuries: 49.4% (Cervical injuries: 30.9% and lumbar spine injuries: 19.8%)	[92]
The average duration of rehabilitation (days)	169 ± 85.72	[92]	126 ± 80.13	[92]
The mean FIM efficiency (points/day)	0.19 ± 0.18	[92]	0.25 ± 0.18	[92]