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Pediatric Spinal Cord Injury: The Challenges of Injury Modelling and Translation to the Clinic

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Spinal cord injury (SCI) is a devastating condition that can arise from mechanical trauma to the spinal cord, or from a variety of non-traumatic insults, such as infection, oncogenesis, birth trauma, and electrocution [1]. Regardless of the cause, SCI will result in either complete or partial loss of motor and sensory function below the lesion site [2], as well as some degree of autonomic dysfunction [3]. SCI will often result in severe loss of tissue and varying degrees of functional impairment, and, after SCI, the spinal cord exhibits only limited repair [4]. This can have debilitating effects on the quality of life, and even the life expectancy, of SCI patients [5].

In the adult population, the majority of SCI results from motor vehicle accidents (MVA) [6]. In infants and children, the common causes of SCI include trauma, resulting from MVA and sports injury, but also from infections, neoplasms, congenital malformations, and birth trauma [7]. The majority of SCI occur at the cervical level [2], resulting in more severe autonomic dysfunction and a greater loss of function in the body than a similar injury lower in the cord. SCI has a high cost to the community, both financially and socially, although there is a lack of accurate epidemiological data available in many countries [1]. A 2007 estimate of the global incidence of spinal cord injury resulting from trauma (TSCI) was 23 cases per million population each year [1]. Less is known about pediatric SCI, as it is rarer, accounting for only 1-13% of all SCI [7-10]; however, pinning down an exact figure is difficult as different studies use different age ranges and different parameters to assess the injury based on hospital admissions, ASIA score and associated co-morbidities [7-10]. In the pediatric SCI population, the majority of injuries result from non-traumatic SCI, with traumatic spinal cord injury (TSCI) being much less common [7].

SCI has a biphasal pathophysiology consisting of the primary, immediate injury and a prolonged, exacerbating secondary injury phase [18-21]. There is little that can be done in the primary injury phase and the secondary damage phase of SCI is complex and changes over time, making it difficult to identify a simple therapeutic target to alleviate its detrimental effects. This injury phase involves multiple mechanisms and systems, not the least of which is the inflammatory response, however we still have little understanding of how these may differ between mature and pediatric patients and animal models. The inflammatory response plays a significant role in the profile of the microenvironment of the lesion after SCI, as do the actions of reactive astrocytes and activated endogenous microglia [22]. This basic pathophysiology is common to SCI in both adult and developing cords. The majority of SCI research has been carried out in animal models with a variety of different mammals used in adult models, including non-human primates. Pediatric models have used pigs [23], cats [24-26], and possums [27] as well as the common use

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of mice [28-30] and rats. This has given a broad view of the similar response in a wide range of mammals, although little has been corroborated in humans. However, as mammals, it is thought that humans will exhibit a similar response to that of the experimental animals used in research [31]. The developing spinal cord exhibits significant difference to the fully developed adult cord in a variety of aspects, from biomechanical [32-34], cellular and structural [23,35,36] to molecular [28,37-39]. There is also a trend for infants having a better recovery from analogous injury than their adult counterparts, that bears greater scrutiny [14,32,35,40,41].

All of this causes some difficulty in exploring SCI in the pediatric population experimentally. Despite the prevalence of non-traumatic SCI in the pediatric population the vast majority of work exploring pediatric SCI is performed using traumatic models of injury. This is due to the complexities in creating an infant model; traumatic models are logistically easier, more readily reproducible and comparable to similar models in adults. We also have only a limited understanding of the analogous ages between the model animals and human development, as well as the developmental timing. The developmental timing, and especially the landmark development stages, are poorly understood in our model animals which creates difficulty in aligning these models with the same landmarks in human development. This alignment is necessary to account for the impact that the development of the spinal cord, CNS and exogenous systems is having on the response to a SCI in the pediatric population. To further validate these models, allow for greater utility in studying the pathophysiology of SCI and for the development of potential therapies a deeper understanding of the model animals themselves is essential.

The 'normal' behavior of infant and neonatal animals is inherently different to that in fully developed adults, and changes with different stages of development, which also adds another layer of complexity to analyzing models of pediatric SCI. In a pediatric model of SCI, it is hard to accurately ascertain where development ends and recovery begins. Very little is known about how much of an impact the developmental state and plasticity of young spinal cords has on injury recovery and the potential of 'rewiring' around the injury. This is further complicated by the presence of central pattern generation in the spinal cord. Central pattern generation allows for the development of reflex movements, without significant input from descending pathways and is common in infant animals. This complicates the assessment of locomotor function in these animals after injury.

SCI in the pediatric population may be rarer, however it is an injury that incurs literally 'life-long' ramifications. Unfortunately, we still understand very little about how the developing spinal cord responds to injury, or how the state of development affects this response. Pediatric SCI is quite a unique injury and therefore presents unique challenges on a clinical level, as well as ongoing challenges for the patient due to its great effect on ongoing physical and psycho-social development [42]. Injury presentation and aetiology of pediatric SCI is different to that in mature adults on a basic and clinical level, and a greater understanding of the mechanisms behind SCI in younger subjects is needed to assist in the clinical management of these patients. The development of clinically relevant animal models is challenging and still requires substantial exploration. While current traumatic SCI models have found some promising avenues of research and a trend of better recovery in younger animals the developmental and behavioral complexities inherent in a pediatric model of SCI need to be addressed. And finally, a greater effort needs to be devoted to finding models to understand the progression of non-traumatic injuries as well as the post-injury sensory and autonomic impacts.

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