A Narrative Review of Pediatric Nontraumatic Spinal Cord Dysfunction

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This article provides a narrative review of seven key issues relevant to pediatric onset of spinal cord damage not due to trauma, or spinal cord dysfunction (SCDys). The first topic discussed is terminology issues. There is no internationally accepted term for spinal cord damage not due to trauma. The implications of this terminology issue and an approach to addressing this are discussed. Second, a brief history of SCDys is presented, focusing on conditions relevant to pediatrics. Third, the classification of SCDys is outlined, based on the International Spinal Cord Injury Data Sets for Non-Traumatic Spinal Cord Injury. Following this, a summary is given of the epidemiology of pediatric SCDys, primarily focused on the incidence, prevalence, and etiology, with a comparison to traumatic spinal cord injury. Next, important clinical rehabilitation principles unique to children with SCDys are highlighted. Then important prevention opportunities for SCDys in children are discussed. Finally, trends, challenges, and opportunities regarding research in SCDys are mentioned. **Key words:** pediatric, rehabilitation, review, spinal cord diseases, spinal cord injury

Spinal cord damage not due to trauma, referred to here as spinal cord dysfunction (SCDys), has many heterogeneous causes.^{1,2} The most common reported etiologies in adults are degenerative spinal conditions, benign or malignant tumor, vascular problems resulting in an infarction or hemorrhage, infections, and inflammation.¹⁻³ In adults, SCDys is associated with older age; the typical median age is 60-65 years old.^{1,3,4} Compared with traumatic spinal cord injury (SCI), there are fewer publications on SCDys, with only a small proportion of these involving pediatric SCDys. In recent years, there has been increasing recognition of the need to address the imbalance against SCDys in clinical services and research.

The aim of this article is to present a narrative review of seven key issues relevant to pediatric SCDys. This content is based on the Newton C. McCollough Lecture, part of the 2018 Howard H. Steel Pre-course held prior to the International Spinal Cord Society conference, on September 12, 2018, Sydney Australia, which was presented by the author. The lecture was based on previous

publications involving the author^{2,5-10} and is summarized here. No systematic review of the literature was performed for this article or the lecture, but the publications all involved a review of the relevant literature during their preparation.

The first issue discussed is terminology. There is no internationally accepted term for spinal cord damage not due to trauma, and many different terms have been used to describe these conditions.⁵ The implications of this terminology issue and an approach for improving this are discussed. Second, a brief history of SCDys is presented,⁶ focusing on conditions relevant to pediatrics. Third, the classification of SCDys is outlined, based on the International SCI Data Sets for Non-Traumatic SCI.² Following this, a summary is given of the epidemiology of pediatric SCDys, primarily focused on the incidence, prevalence, and etiology, along with a comparison to SCI.¹⁰ Next, important clinical rehabilitation principles unique to children with SCDys are highlighted.⁷ Then important prevention opportunities for SCDys in children are discussed.⁸ Finally, trends, challenges, and opportunities regarding research in SCDys are mentioned.⁹

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Terminology Issues

There is no internationally accepted term for spinal cord damage not due to trauma. Many different terms have been used in the literature to describe these conditions, including non-traumatic spinal cord injury, spinal cord damage, spinal cord dysfunction, spinal cord lesion, medical paraplegia, myelopathy, and spinal cord myelopathy.⁵

The MEDLINE and EMBASE classification systems for medical search terms and the Center for Disease Control and Prevention in the United States¹¹ define SCI as only due to traumatic conditions. In addition, MEDLINE and EMBASE use “spinal cord diseases” as the global term for both traumatic and nontraumatic spinal cord damage. The absence of an accepted term for spinal cord damage not due to trauma negatively impacts the ability to identify relevant publications when searching the literature.⁵ Furthermore, participants from different studies may not be comparable if different terms and inclusion criteria are used, restricting the generalizability of research and the ability to pool results.⁹

An international consensus process has been proposed as a pathway to adopt an agreed term for nontraumatic spinal cord damage^{5,12} and to consider the appropriateness of “spinal cord diseases” as the global term for traumatic and nontraumatic spinal cord damage. This process has commenced and currently involves the International Spinal Cord Society (ISCoS), the American Spinal Injury Association (ASIA), and editors of *Spinal Cord*, *Spinal Cord Series and Cases*, *Journal of Spinal Cord Medicine*, and *Topics in Spinal Cord Injury Rehabilitation*, with plans to include other stakeholders as they are identified.

History of SCDys

There is evidence suggesting that spina bifida has existed since the origins of humans.¹³ Hippocrates (460-377 BCE) believed that cold and moisture were associated with paraplegia,¹⁴ and this belief was held by some until the 16th century.¹⁵ Hippocrates, however, was also the first to describe SCDys due to infection, possibly from tuberculosis.¹⁴

Improved knowledge regarding the pathophysiology of conditions that cause SCDys started to develop as the understanding of neuroanatomy improved. It was not until 1866 that it was recognized that the spinal cord could be damaged by circulation disturbances as well as inflammation, but debate on this persisted for some time.¹⁶ In the later 19th century, advances in the understanding of the blood supply of the spinal cord¹⁷⁻¹⁹ were pivotal in increasing our understanding of the neuroanatomical basis for infarction and vascular malformations. It was not until 1921 that the distinction between myelitis and myelomalacia was clarified.²⁰ Only in the 20th century were neurological disorders classified into the broad categories of trauma, infections, vascular, nutritional, degeneration, inflammatory or demyelinating, and hereditary.²¹ These categories, with the exception of trauma, form the basis of the recommended classification of the etiology of SCDys.²

Highlights in the history of SCDys regarding the diagnosis and management of etiological conditions have been discussed in detail previously.⁶ Some key highlights in the history of SCDys relevant to pediatrics are summarized below.

Congenital

Archeological evidence suggests that spina bifida has existed as long as humanity,¹³ and a description of spinal bifida was given by Hippocrates.²² The first definitive depiction of spina bifida was by the Dutch clinician Peter van Forest in the late 1500s.²³ Nicholaas Tulp coined the term “spina bifida” in 1641.²⁴ For many decades the surgical treatment of spina bifida involved ligation or amputation of the dural sac, with very poor outcomes.¹³ By the early 20th century, improved surgical techniques emerged, with multilayer closure advocated by Charles Frazier in 1918.²⁵ In 1967 Sharrard demonstrated that outcomes were improved by performing surgery in the perinatal period,²⁶ which is now routine practice.

Tumor

The first successful resection of an intradural tumor was by Sir Victor Horsley in 1887.²⁷ The first resection of an intramedullary spinal cord tumor was by Christian Fenger in 1890.²⁸ For many decades,

however, the complication rate was extremely high and many neurosurgeons recommended a conservative approach, with biopsy, dural grafting, and radiation therapy, regardless of histological diagnosis. During the latter half of the 20th century, major surgical developments occurred that significantly improved outcomes for patients with spinal cord tumors.²⁹ The benefits of radiotherapy for spinal tumors were demonstrated by Wood in the 1950s,³⁰ and radiotherapy is now routine for many primary and secondary spinal cord tumors, often in conjunction with surgery.³¹

Infections - viral

Michael Underwood provided descriptions of what was possibly poliomyelitis in 1789,³² but Jakob von Heine provided the first detailed description in 1840, subsequently naming the condition.³³ Oskar Karl Medin was the first to highlight the epidemic nature of the disease in 1890.³⁴ Many epidemics affected hundreds of thousands of people around the world during the 20th century, peaking during the 1940s and 1950s. An inactivated poliovirus vaccine was developed by Jonas Salk in 1952,³⁵ and subsequently Albert Sabin developed an oral polio vaccine.³⁶ These two vaccines have virtually eradicated polio from most countries around the world.³⁷

Inflammatory - transverse myelitis

For centuries “myelitis” was used as a general term for a wide range of conditions, including inflammatory and ischemic, without an appreciation of pathophysiological mechanisms.^{38,39} Since the middle of the 20th century, the current differentiation became well established.⁴⁰ It is now well known that a wide range of autoimmune, inflammatory, and infectious etiologies can cause transverse myelitis. The acute management is directed by the suspected etiology, with rapid initiation of the appropriate treatment increasing the likelihood of improved outcomes.^{41,42}

Classification of SCDys

The International Spinal Cord Injury Data Sets for Non-traumatic Spinal Cord Injury consist of a basic and extended data set² and include a classification

system for the many heterogeneous causes of SCDys based on a two-axis approach. The first axis uses a two-tier (congenital-genetic and acquired), five-level hierarchy. The hierarchy allows for an increasing level of detail regarding the classification of the etiology. The basic level of the data set (**Table 1**) classifies the etiology of SCDys using axis 1 to the second level. Levels of classification can be collapsed where there are few patients in the sample with these conditions, for example, congenital and genetic, and expanded to additional levels of detail for more frequent causes. For example, neoplastic (level 2) – malignant (level 3) – neural (level 4) – astrocytoma – malignant (level 5).

Additional items in the dataset include the timeframe of the onset of SCDys symptoms (acute [≤ 1 day], subacute [≤ 1 week], prolonged [> 1 week – month], and lengthy [> 1 month]). The extended dataset also includes a record of any iatrogenic component in the etiology. The axis 2 of the classification uses the International Statistical Classification of Diseases (ICD) to code the initiating disease, condition, or process that caused the SCDys. It is recommended that the nontraumatic datasets be used for classifying the etiology of SCDys in clinical practice and research to facilitate improvement in comparative research, especially epidemiological and prevention studies. Complete instructions for data collection, data sheet, and training cases are available at the websites of ISCoS (<http://www.iscos.org.uk>) and ASIA (<http://www.asia-spinalinjury.org>).

There has been some validation of the International SCI Data Sets for Non-traumatic SCI classification of etiology, with a retrospective study of over 900 adults finding that only 4% of cases were not able to be classified or were unknown.³ Further validation studies using prospective methodology, and in children, are required.

Global Epidemiology of Pediatric Spinal Cord Damage

Compared with adults, there is relatively little study of the epidemiology of pediatric spinal cord damage from any cause, both SCI and SCDys. A recent systematic review of the epidemiology of pediatric spinal cord damage

Table 1. Classification of spinal cord dysfunction etiology²

Tier	Level 1	Level 2
Congenital - genetic	Congenital	Spinal dysraphism Arnold-Chiari malformation Skeletal malformations Other congenital
	Genetic disorders	Hereditary spastic paraplegia Spino-cerebellar Adreno-myeloneuropathy Other leukodystrophies Spinal muscular atrophies Genetic – other
Acquired	Acquired abnormalities	Vertebral column degenerative disorders Metabolic disorders Vascular disorders Inflammatory and auto-immune diseases Radiation related Toxic Neoplastic Infection Miscellaneous

included a literature search of MEDLINE (1946 – March 2017) and EMBASE (1974 – March 2017) for epidemiological studies involving pediatric spinal cord damage.¹⁰ The search identified 866 potentially relevant articles, from which 25 articles were included, from 13 countries in six of the 21 global regions. There were 14 studies regarding pediatric SCI and seven on SCDys. An additional four articles provided both SCI and SCDys data. There was a scarcity of quality epidemiology studies, especially from non-developed regions, and the data quality was generally not high. The key epidemiology findings were mapped globally to facilitate comparisons. An age cutoff for inclusion of less than 15 years was planned, but in some instances, because of the paucity of data, publications with age cutoffs less than 19 years were included. A summary of the key findings from the review is given below.

The median SCDys incidence rates for the global regions were Australasia, 6.5/million population/year; Western Europe, 6.2/million population/

year; and North America, high income, 2.1/million population/year. By comparison, the median incidence rates of SCI in the global regions were Asia, east, 5.4/million population/year; Australasia, 9.9/million population/year; Western Europe, 3.3/million population/year; and North America, high income, 13.2 million population/year.

The prevalence rates for SCDys were Australia, 6 per million population in 2010; Canada, 2.5 cases per million population in 2010; and Ireland, 19.6 cases per million population in 2015. In contrast, the prevalence rates of SCI were Australia, average estimate of 51.5 cases per million population in 2011; Canada, 10.1 cases per million population in 2010; and Ireland, 12.1 cases per million population in 2015.

There were only a few studies on survival following spinal cord damage, with the overwhelming majority having very small sample sizes. The only studies of survival in children with SCDys involved tumors, and all had small sample sizes. The best study on survival following SCI, from the United

States, reported that children aged less than 16 years at the time of injury had their annual odds of dying increased by a third compared with people injured at an older age.

SCDys was mostly due to tumors (30%-63%) and inflammatory/autoimmune causes (28%-35%). SCI was mostly caused by land transport (46%-74%), falls (12%-35%), and sport or recreation (10%-25%). There were few studies where the level of spinal cord damage was detailed, with most reporting SCI and SCDys more likely to result in paraplegia.

Important Clinical Rehabilitation Issues Unique to People With SCDys

Most aspects of rehabilitation following SCI or SCDys are the same for each group. There are, however, a number of unique issues regarding the rehabilitation of people with SCDys. It is important for clinicians to be aware of these unique issues in order to optimize the rehabilitation outcomes for people with SCDys, and these have been discussed in detail previously.⁷ These issues unique to people with SCDys include classification, general rehabilitation, etiology-specific, and the role of the rehabilitation physician as a diagnostic clinician. The main issues relevant to the rehabilitation of pediatric SCDys patients are summarized here.

Classification issues unique to people with SCDys

The classification issues regarding SCDys are the classification of etiology and neurology. The classification of etiology of SCDys is discussed above. The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) were initially developed for SCI.⁴³ Many authors have used them in adults with SCDys,^{3,44,45} even though they are yet to be validated in these patients. It is believed, however, that there is no reason why the ISNCSCI should not be used for describing the neurological impairment in people with SCDys,^{7,9} including children. Furthermore, there is no validated alternative. In addition, it is important to note that it is not appropriate to use the ISNCSCI in children younger than 6 years old.⁴⁶

General rehabilitation issues unique to people with SCDys

Predicting neurological improvement, rehabilitation outcomes, and survival

Predicting neurological and rehabilitation outcomes following SCDys is very difficult and challenging.⁷ The grade and level of spinal cord damage influences the rehabilitation outcomes. Typically, SCDys results in an incomplete grade of spinal cord damage.^{47,48} As a result, it can be quite difficult, especially in the early period, to know which patients with SCDys will improve in their neurology. Another challenge to predicting improvement is that some conditions causing SCDys are progressive.

Participation in rehabilitation

Some conditions that cause SCDys require ongoing treatments during rehabilitation, for example, plasma exchange, intravenous immunoglobulin, or immunosuppressant medications. With optimal planning, these treatments can be delivered alongside rehabilitation therapy. Children with tumors often need radiation therapy and/or chemotherapy; scheduling these to minimize the impact on rehabilitation care is essential.

Etiology-specific issue: nontraumatic SCDys due to tumor

Benign and malignant tumors are the most common etiology of SCDys in children.¹⁰ The dual diagnosis of having a tumor causing SCDys creates major challenges for the child, their family, and the rehabilitation team. Practical recommendations for rehabilitation teams regarding the management of people with SCDys due to tumor have been detailed,⁴⁹⁻⁵² and these apply equally to children as well as adults. Key aspects of these recommendations are summarized below.

An acronym, NOMPRS, gives a framework for recommendations regarding the rehabilitation of people with SCDys due to tumors.^{49,50} This stands for **N**eurological, **O**ncologic, **M**edical, **P**ain, **R**ehabilitation, and **S**upport status of the patient. The outline of NOMPRS is as follows:

N: Neurological status. More complete spinal cord damage has a lower probability of improvement.⁴⁷ If the tumor is progressive, it is important to anticipate functional decline.

O: Oncologic status. This determines the survival, which differs markedly between tumor types, however there is also very wide variation within the same tumor group.

M: Medical comorbidities. If present, these can have a marked impact on participation in rehabilitation and necessitate optimal management.

P: Pain is common and multifactorial, and a thorough assessment is required to diagnose the cause(s) and devise management strategies.

R: Rehabilitation issues. This includes a length of stay for inpatient rehabilitation that is as short as possible, with many goals deferred to community rehabilitation, based on prognosis. Those with a worse prognosis have a greater emphasis on a shorter stay in rehabilitation. Children with a very good prognosis or presumed cured do not need any shortening of their rehabilitation.

S: Social supports. These have a crucial influence on discharge planning. The parent(s) and family have a vital role, and financial resources can also help significantly.

Rehabilitation physician as a diagnostic clinician

Physiatrists working with children who have SCDys have a role as diagnostic clinicians to identify the correct diagnosis where there is a possibility of a missed or incorrect diagnosis. Occasionally there are children with SCDys who come under the care of a physiatrist, either in a clinic or inpatient unit, with an uncertain diagnosis regarding their SCDys or with an incorrect diagnosis. A physiatrist can formulate a differential diagnosis not previously contemplated and initiate investigations while progressing functional rehabilitation.⁷

Prevention of Nontraumatic SCDys

Compared with SCI, there has been limited involvement of the international spinal cord medicine community in research or intervention programs directed at the prevention of SCDys.

The reasons for this and a detailed discussion of current programs and future potential opportunities have been published.⁸ As with traumatic SCI, not all SCDys can be prevented. There are, however, opportunities for the prevention of SCDys in the pediatric age group that are briefly summarized here.

Prevention of spina bifida

There is overwhelming evidence that periconceptional supplementation with daily folic acid prevents spina bifida,⁵³ and this is a low-cost intervention.⁵⁴ Unfortunately, however, many low resource countries with insufficient health care resources to implement supplementation also lack adequate health care resources to manage the lifelong consequences of spina bifida.

Prevention of tumors causing SCDys

For anyone with a suspected spinal tumor, the ideal care involves prompt magnetic resonance imaging and other diagnostic investigations. Secondary malignant tumors need surgery and/or radiotherapy within the first 48 hours of symptom onset to reduce the risk of progression from bony lesions to symptomatic SCDys and to reduce the severity of the neurological impairment.⁵⁵ Unfortunately, many patients experience a delay in the diagnosis and treatment of spinal tumors and progress to SCDys, especially in low resource countries.

Prevention of infections that cause SCDys

There are opportunities for the prevention of SCDys due to infections. Rapid access to radiological imaging, neurosurgery if appropriate, and appropriate antibiotic, antiviral, or antiparasitic treatments, as indicated, are important principles.^{56,57} Improving access to these would reduce the incidence of infectious causes of SCDys as well as improve other patient outcomes.

Screening and subsequent prompt appropriate treatment of tuberculosis bacillus infections, especially spinal column disease before cord compression develops, are effective in reducing SCDys.⁵⁸⁻⁶⁰ In many developing countries,

especially in Africa and Southeast Asia, this is a common cause of SCDys.⁵⁹ It is anticipated that global polio vaccination will eventually eliminate poliomyelitis as a cause of SCDys.⁶¹ Currently, polio remains endemic in Nigeria, Afghanistan, and Pakistan (<http://www.polioeradication.org/infectedcountries.aspx>).

Trends, Challenges, and Opportunities Regarding Research in Nontraumatic SCDys

There has been a considerable increase in publications on SCDys over the past four decades, from 1,825 (1974-1983) to 11,887 (2004-2013). There has also been an improvement in research methodology over this period, with a trend away from case series/small sample size, single-center, retrospective studies to studies that have a larger sample size, are multicenter, longitudinal, and/or prospective.⁹ This trend needs to continue in order to optimize the quality of research in SCDys.

Challenges to SCDys rehabilitation research and opportunities for addressing these have been reported and grouped into three themes: identification of cases; study design and data collection; and other – funding, preclinical, and international research.⁹

Identification of cases

The issue regarding the absence of an internationally accepted term for spinal cord damage not due to trauma is relevant to note again here.

Researchers have used the ICD codes to identify patients with SCDys from health databases for research purposes.^{12,62,63} Given the rarity of SCDys, population-based studies using health databases that code etiology using the ICD codes are an important source of research data for this group. However, a challenge for researchers is that there is no single ICD-10/11 code specifically for SCDys, and there is no accepted gold standard list of codes for the various conditions causing SCDys. Modifications to ICD coding conventions for

conditions relevant to SCDys are recommended, along with greater use of population datasets for research.⁹

Study design and data collection

The issues regarding ISNCSCI use in people with SCDys and the previous lack of an agreed classification of etiology are relevant matters. SCDys is a rare condition (as is SCI), which challenges the recruitment of large numbers of participants for research. In addition, many registries and research projects exclude those with SCDys. Efforts are required to improve recruitment of SCDys in research, facilitate multicenter studies that include SCDys, and lobby for their inclusion on patient registries.

Other issues: funding, preclinical studies, and international issues

Funding for research involving SCDys is more difficult to obtain than for SCI, and it is important to enhance the quality and quantity of research in this area. Molecular-level and animal studies emphasize SCI, with little research in these fields occurring in SCDys conditions,^{64,65} and this also is important to improve. International guidelines for conducting clinical trials do not consider SCDys, the framework of research guidelines implicitly refers to SCI,⁶⁶ and it is recommended that this framework be adjusted to including appropriate subgroups of patients with SCDys (eg, those with non-progressive causes). Barriers and enablers for international collaboration in SCI have been described, and these are just as relevant, if not more so, for research in SCDys.⁶⁷

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