Trends, Challenges, and Opportunities Regarding Research in Non-traumatic Spinal Cord Dysfunction

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Background: Spinal cord dysfunction (SCDys) is caused by heterogeneous health conditions, and the incidence is increasing. Despite the growing interest in rehabilitation research for SCDys, research into SCDys faces many challenges. **Objective:** The objective of this project was to perform a clinical review of changes in SCDys research over the last 4 decades; identify challenges to conducting research in SCDys; and propose opportunities for improving research in SCDys. **Methods:** A triangulation approach was used for obtaining evidence: literature search (January 2017) using MEDLINE and Embase databases for publications in English (1974-2016) regarding SCDys; workshop discussions at the International Spinal Cord Society annual meeting, September 16, 2016, Vienna, Austria; and our collective expertise in SCDys clinical rehabilitation research. **Results:** There has been a substantial increase in publications on SCDys over the 4 decades, from 1,825 in 1974-1983 to 11,887 in the decade 2004-2013, along with an improvement in research methodology. Numerous challenges to research in SCDys rehabilitation were grouped into the following themes: (a) identification of cases; (b) study design and data collection; and (c) funding, preclinical, and international research. Opportunities for addressing these were identified. **Conclusions:** The increase in scientific publications on SCDys highlights the importance of this heterogeneous group among the research community. The overall lack of good quality epidemiological studies regarding incidence, prevalence, and survival in these patients serves as a benchmark for guiding improvements to inform evidence-based care and policy. **Key words:** epidemiology, health services, rehabilitation, research, spinal cord diseases, spinal cord dysfunction, spinal cord injury

The incidence of non-traumatic spinal cord dysfunction (SCDys) is higher than that of traumatic spinal cord injury (SCI) in many developed countries, with the best evidence coming from Australia and Canada.^{1,2} However, there is an overall paucity of studies on the epidemiology of SCDys.³ The causes of SCDys are varied and heterogeneous^{3,4}; the most common causes are reported to be degenerative conditions of the spinal column, benign or malignant tumor, vascular problems resulting in an infarction or hemorrhage, infections,

or inflammation.³⁻⁵ SCDys is associated with an increased age; the typical median age is 60 to 65 years.^{1-3,5} One study estimated that half of the causes of SCDys are due to age-related conditions.⁶ With population aging, it is projected that in most regions of the world, the proportion of the population aged over 65 years will double between 2000 and 2050.⁷ As a result, it is anticipated that the incidence of SCDys will increase dramatically¹ and potentially overwhelm health and community services, including spinal cord rehabilitation services.

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Over the past decades, there has been growing research interest in SCDys. However, there are unique challenges for research regarding persons with SCDys that have not been extensively discussed in the literature. In light of this, the objectives of this paper are to (a) review and discuss changes in SCDys research over the past 4 decades, including changes in the number and type of publications; (b) identify challenges to conducting research in SCDys; and (c) propose opportunities for improving research in SCDys.

Methods

The identification of changes in SCDys research over time, challenges for research, and opportunities for improvement in this population were based on a triangulation approach, using 3 methods: (1) the results of a literature search; (2) discussions that occurred during a workshop at the International Spinal Cord Society 55th Annual Scientific Meeting, September 14, 2016, Vienna, Austria; and (3) our collective interdisciplinary expertise in undertaking clinical research regarding the rehabilitation of people with SCDys. These strategies were used to inform the results presented below.

Literature search

Change in the number of spinal cord dysfunction publications over time

An electronic literature search was conducted (January 2017) using MEDLINE and Embase databases (1974–2013) for publications regarding SCDys, including the most common reported causes of these conditions (degenerative conditions, benign or malignant tumor, vascular problems resulting in infarction or hemorrhage, infections, or inflammation). Embase was only available for searching from 1974 onwards. There would have been very few relevant publications prior to this time, and we wanted to include both MEDLINE and Embase databases for the same time period. The terms used in the literature search were the same as those used in a previously published gold standard comprehensive search strategy for SCDys.⁸ Only publications involving humans were included, but there was no language

restriction. We planned to compare the number of publications identified across the 4-decade periods that the search was conducted. For comparison purposes, a search was performed for publications on traumatic SCI over the same time period using the search term “Spinal Cord Injury/” and the same exclusions.

Change in nature of spinal cord dysfunction research over time

To examine changes in SCDys research over time, we selected a convenient sample of publications from the literature to characterize the type and quality of research and how it changed over time.

Publications regarding barriers and challenges to spinal cord dysfunction research

The focus of this search was to identify publications that discuss research challenges and opportunities for SCDys. The articles identified by the gold standard comprehensive search strategy for SCDys publications,⁸ described above, were combined with the search terms “barrier*” OR “challeng*” AND “research”. Only publications in English were included, but there was no restriction on the study design. The search period was restricted to the years 2000 to 2016, because prior to this date there would be very few publications of relevance. We screened the publications identified by the above process by reviewing the title and abstract; if potentially relevant, the full text was reviewed. The processes involved are summarized in **Figure 1**. Our personal libraries were also searched for potentially pertinent publications, and the reference section of all the included publications were reviewed for any additional relevant articles.

Conference workshop

A workshop titled “Identification of Cases of Non-traumatic Spinal Cord Disorder Using Administrative Databases: Rationale, Approaches and Challenges” was led by some of the authors (P.W.N., S.B.J., S.J.T.G., C.H.H.) at the International Spinal Cord Society 55th Annual Scientific Meeting, September 14, 2016, Vienna, Austria

Figure 1. Flow chart of the search methodology and overview of results regarding research barriers and challenges for spinal cord dysfunction.

(http://www.iscos.org.uk/uploads/ABSTRACTS/ISCoS_2016_ABSTRACT_BOOK.pdf). The 1.5-hour workshop included presentations on the following components:

- Historical perspective of non-traumatic spinal cord disorder research⁹ and the Australian experience with identifying non-traumatic spinal cord disorder using administrative data
- Decisions, decisions: Algorithms for identifying non-traumatic spinal cord disorders^{10,11}
- Demographic and clinical characteristics of cases of non-traumatic spinal cord disorder¹²

- Who are we missing? Comparing cases in administrative data with chart review

The workshop presentations highlighted the barriers to conducting research in SCDys and opportunities for improvement. The presentations were followed by an interactive 30-minute audience and panel discussion, which highlighted additional challenges.

Results

Change in the number of SCDys publications over time

There was a notable increase over the 40 years from 1974 to 2013 in the number of publications regarding both SCDys and SCI (1974-1983: SCDys = 1,825, SCI = 1,528; 2004-2013: SCDys = 11,887, SCI = 16,750). In the past decade, however, there were more publications on SCI than SCDys (see **Figure 2**).

Change in nature of SCDys research over time

There has been a change in the nature and number of publications regarding SCDys rehabilitation outcomes over the years. Early reports tended to be case studies or small sample studies from single units.^{6,13-20} Studies continue to be published with small samples from single centers.²¹ Subsequently, retrospective and prospective studies have been published with larger sample sizes, in cross-sectional as well as longitudinal studies; however these were also from single centers.²²⁻²⁵ Lately, multicenter studies have emerged, from both within a single country²⁶⁻³² and internationally.^{5,33,34}

Until recently, studies described the etiologies of SCDys using different classification systems, with the authors formulating their own classification systems due to the lack of an internationally accepted consensus classification system for SCDys. This limited the ability to compare results across different studies. Due to this lack of standardization, an international collaboration has developed a number of datasets for use in patients with SCI or SCDys to facilitate meaningful comparison between study results and adjust for sources of bias.³⁵ The International SCI Core Data Set includes the etiology of SCI classified into 7 categories, one of these being SCDys without any

Figure 2. Changes over 40 years in the number of MEDLINE and Embase publications on spinal cord injury (SCI) and spinal cord dysfunction (SCDys).

further categorization of the numerous possible causes.³⁶ To address this lack of standardization, an International Data Set for Non-traumatic SCDys, including a classification system for the causes, was developed.⁴ The classification system uses a hierarchal approach, with a 2-tier (congenital-genetic or acquired) 5-level system that allows for increasing specificity of detail regarding etiology. The development of this classification system was critical to facilitate comparisons between different studies and for pooling findings from different groups.⁵ A revision of the International SCI Core Data Set³⁷ acknowledged this limitation; an expansion of the classification of non-traumatic SCDys includes 7 options based on the first 2 levels of the International Non-traumatic SCI Dataset.⁴

In the absence of standardization of case identification, high-quality epidemiological studies regarding incidence, prevalence, and survival studies are challenging to produce for this population. Recently, a global mapping of

the epidemiology of SCDys was carried out and highlighted the challenges with epidemiological data for this population.³

Publications regarding barriers and challenges to SCDys research

The electronic search of the literature for publications on barriers and challenges to research in SCDys identified 61 articles after combining the previously published gold standard comprehensive search strategy for SCDys and the search terms (“barrier*” OR “challenge*” AND “research”). Five articles were retained for detailed review after screening title and abstract. Only one relevant publication was retained after a detailed review of these 5 papers (see **Figure 1**).³¹

Challenges to conducting research in SCDys

Numerous barriers and challenges to research in SCDys were identified and grouped into the following

Table 1. Summary of challenges and opportunities in research on non-traumatic spinal cord dysfunction

Challenges in non-traumatic spinal cord dysfunction research	Opportunities in non-traumatic spinal cord dysfunction research
Identification of cases	
Lack of internationally accepted terms for spinal cord damage not due to trauma	An international consensus process is needed to adopt an agreed term for non-traumatic SCDys.
Lack of specific International Classification of Diseases–10 codes for SCDys	Changes are proposed to the International Classification of Diseases–10 regarding SCDys.
Study design and data collection	
Some cases of SCDys have gradual onset of symptoms.	Accepted definition of classifying patterns of symptom onset and criteria for date of onset
ISNCSCI has not been validated for SCDys.	Formal validity study of the ISNCSCI in people with SCDys
Recruitment of participants for research	Further validation and possible refinements of the International Non-traumatic SCI Data Sets
SCDys is relatively rare, with heterogeneous etiologies that influence outcomes. Acute hospital management of SCDys is decentralized.	Multicenter studies and longitudinal studies involving a larger number of people with SCDys
Rehabilitation of SCDys is decentralized – most are not admitted to specialist units.	Increasing range of research variables, particularly environmental and population characteristics
Many registries exclude patients with SCDys.	Utilize more advanced statistical methods
Very few multicenter studies	
Other issues: funding, preclinical, and international research	
Obtaining research funding is very challenging.	Improve the funding of research into SCDys.
Very little preclinical research focuses on SCDys	Develop additional animal models of SCDys.
International guidelines for conducting clinical trials do not consider SCDys.	Increase preclinical research into SCDys.
	Include people with SCDys in clinical intervention studies in acute phase and rehabilitation.
	Revise international guidelines for clinical trials in SCI to facilitate inclusion of SCDys.
	Spinal cord registries should explore ways of including people with SCDys.
	Explore collaboration with national and international groups involved with research into SCDys.

Note: ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury; SCDys = spinal cord dysfunction; SCI = spinal cord injury.

themes: (a) identification of cases; (b) study design and data collection; and (c) funding, preclinical studies, and international research (see **Table 1**).

Identification of cases

Definitions and related issues. There is no internationally accepted term for spinal cord damage not due to trauma. Terms used in the literature to describe these conditions include non-traumatic spinal cord injury, spinal cord damage, spinal cord dysfunction, spinal cord lesion, medical paraplegia, myelopathy, and spinal cord myelopathy.⁸ SCI is defined as a traumatic

condition according to the Centers for Disease Control and Prevention,³⁸ and the MEDLINE and Embase databases also define SCI as a traumatic condition. One important implication of the lack of an accepted term for spinal cord damage not due to trauma is that it has an adverse impact on the ability to identify all potentially relevant publications when performing a comprehensive literature search.⁸ Another implication is that study participants may not be comparable if different definitions are used for inclusion criteria, and this restricts the generalizability of research.

One aspect of the complexity of SCDys that influences research is the determination of

when SCDys occurs. This applies specifically to individuals with a more gradual onset of neurological symptoms, such as tumor, infections, and degenerative conditions of the spinal column, that can emerge over weeks or even months.

International Classification of Diseases codes and administrative datasets. A number of researchers have used the International Classification of Diseases (ICD) codes to identify patients with SCDys from state or national databases for research purposes.^{1,31} There is no defined group of ICD-10 codes specifically for SCDys and no accepted gold standard list of ICD-10 codes; there are varying ICD-10 coding conventions for these conditions.¹ This limits the utility for using ICD-10 codes to identify patients with SCDys in many countries. By contrast, traumatic SCI has a more consistent ICD-10 coding convention, although it also has many etiologies.

There are general limitations when using administrative datasets for research that have been discussed previously.³⁹ These include limited clinically relevant context and patient experience data; varying scope and definitions of terminology with concerns related to data quality; restricted timeframes; inability to provide strong evidence for a causal relationship between variables due to unmeasured confounders; data access issues, including approval processes, consent, and legal; and underrepresentation of certain populations (eg, only captures people who access the health system).

Despite these limitations, there are numerous advantages to using data from administrative datasets for research in general⁴⁰ and for persons with SCI or SCDys.³⁹ Some of these advantages include readily available data in an electronic format to facilitate analysis; relative affordability to researchers; ability to identify large numbers of patients, often at a population level, enhancing the generalizability of findings; potential to follow patients longitudinally across different health sectors; ability to provide descriptive reports that are hypothesis generating; and possibility to use record linkages to link multiple datasets.

Study design and data collection

The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)

was originally developed for traumatic SCI.⁴¹ Numerous authors have used it in studies involving people with non-traumatic SCDys,^{5,21,42-45} even though it has not been formally validated in this group. This classification is similar to the Medical Research Council manual muscle testing that was initially developed for lower motor neuron conditions following war injuries and poliomyelitis⁴⁶ but is now used for both upper motor neuron and lower motor neuron conditions.

SCDys is a rare condition (as is traumatic SCI) compared to other conditions such as cancer, diabetes, and cardiovascular disease. As mentioned above, SCDys is also a heterogeneous condition. Consequently, there are challenges with the recruitment of large numbers of participants for research. This applies especially if the desire is to include only one specific cause of SCDys, which is appropriate in some studies because of the differences in outcomes reported between the etiologies.^{43,47}

The acute hospital management of SCDys and rehabilitation services for these people tend to be decentralized; most people with SCDys are not admitted to specialist spinal cord units in acute or rehabilitation hospitals.^{28,29,31,48,49} This creates significant challenges when planning multicenter studies (such as internal and external funding or resource planning and performance monitoring) and makes a population-based registry for these patients extremely difficult. Because of this, many registries exclude patients with SCDys. Until recently, there have been very few multicenter studies, which limits the generalizability of SCDys rehabilitation research findings.⁵⁰ It is also important to acknowledge the referral bias regarding people with SCDys who are referred and admitted to specialist spinal rehabilitation units compared with those who are not referred or admitted to these specialist units, which may influence research findings.

Other challenges for SCDys research: funding, preclinical studies, and international issues

There are other challenges with conducting researching on SCDys that involve funding, preclinical studies, and international research focus. Obtaining funding for research projects involving SCDys is more challenging than for

traumatic SCI; workers' compensation and motor vehicle accident insurance schemes in some regions provide substantial funding for SCI research. Preclinical studies, including molecular-level and animal studies, focus on traumatic SCI; very little research of this nature occurs in SCDys conditions.^{51,52} A recent systematic review of animal studies in SCI identified 2,209 relevant animal studies of SCI, with only 5.5% involving non-mechanical models.⁵³ In addition, international guidelines for conducting clinical trials do not consider SCDys conditions, with the framework of guidelines centered implicitly only on traumatic SCI.⁵⁴ Facilitators and barriers to international collaboration in SCI have recently been reported, and we believe that these apply equally to people with SCDys.⁵⁵

Opportunities for improving SCDys research

The opportunities for improving research in SCDys are categorized below with the same themes that were used for classifying the challenges for research.

Identification of cases

Agreed term for non-traumatic spinal cord damage. An international consensus process is needed to adopt an agreed term for non-traumatic SCDys.^{1,8} This process has commenced and currently involves the International Spinal Cord Society and the American Spinal Injury Association, with plans to include other stakeholders as they are identified.

International Classification of Diseases – coding recommendations. Modifications and refinements to the ICD coding conventions for conditions relevant to SCDys are recommended. This would require international collaboration and take some time to negotiate and implement, however, it would facilitate improvements in the use of administrative databases that use ICD to identify patients with SCDys. We suggest relatively minor modifications in contrast to completely revising all codes relevant to SCDys, as outlined below:

a. *Coding conventions for conditions causing non-traumatic SCDys.* It is suggested that

a coding convention be adopted, which is already established in some countries such as Australia and Denmark, that requires codes to be entered for both the etiology of the SCDys (eg, cord compression from tumor, transverse myelitis and so on) and the neurological consequence (eg, acute paraplegia, acute tetraplegia, or cauda equina syndrome [G82 and G83 codes]).

b. *Prefix or diagnosis type codes.* Patients can have a range of conditions that relate to their hospitalization. These conditions include presenting medical diagnoses, comorbid problems, and complications that occur during the episode of care. It is suggested that a standard coding convention be adopted, with a prefix or diagnosis type to be used in conjunction with the ICD diagnoses codes. This would allow for more contextual information to be captured to better characterize a health system encounter. In particular, we suggest prefixes to indicate the primary reasons for admission for (a) conditions that were present on admission to hospital and that were evaluated and treated, (b) conditions that occurred during the course of hospitalization (complication), or (c) conditions that were preexisting or comorbid that required monitoring, investigation, or treatment during the course of hospitalization.

This convention would facilitate the use of ICD codes to identify those patients who had SCDys on admission of hospital, those who developed it during the course of hospitalization, and those who had SCDys prior to hospital admission and were admitted for management of complications from the SCDys. This would facilitate the use of ICD codes for population-based studies on the incidence of SCDys as well as health resource utilization from hospitalization due to complications from SCDys.

c. *ISNCSCI and ICD.* It is suggested that the severity of spinal cord damage for both traumatic SCI and non-traumatic SCDys be graded using the ISNCSCI.⁴¹

d. *Vascular conditions causing SCDys.* There are numerous vascular conditions that can cause

SCDys.⁴ Current ICD coding for vascular conditions specifies only 2 options:

- G95.1 – Vascular myelopathies
- G95.2 – Cord compression, unspecified

It is suggested that ICD coding for vascular myelopathies be subdivided into those due to infarction and those due to hemorrhage. Although many of the hemorrhagic conditions cause damage via cord compression, it is suggested that it would be appropriate to add a separate code for this group. Furthermore, it is suggested that infarction conditions be subdivided into the following: aortic disease, hypotension-hypoperfusion, idiopathic, other causes not otherwise specified.

- e. *Paraplegia and tetraplegia.* The coding convention for paraplegia and tetraplegia occurring as a result of SCDys (G82) currently has subdivisions into flaccid and spastic types of paralysis. We do not believe that this subdivision is useful or relevant for an administrative database. Furthermore, patients with SCDys can change from flaccid or spastic, particularly in the acute phase. We propose that a better alternative subdivision would be to code separately for acute (onset responsible for current hospital admission) and chronic (occurred prior to current hospital admission) SCDys that results in paraplegia or tetraplegia.
- f. *Cauda equina syndrome.* The coding convention for SCDys resulting in a cauda equina syndrome (G83.4) should be changed to code separately for acute (onset responsible for current hospital admission) and chronic (occurred prior to current hospital admission) cauda equina syndrome.

Study design and data collection

International Standards for Neurological Classification of Spinal Cord Injury validity testing. It is suggested that a formal study needs to be undertaken to determine the validity of the ISNCSCI among people with SCDys and to help with formulating guiding principles that may be appropriate to optimize the validity for

assessing neurological impairment. In the interim, however, it is believed the ISNCSCI should be used for determining the neurological impairment among people with SCDys, accepting the above-mentioned limitation.

International Non-traumatic SCI dataset classification. There has been some validation of the International Non-traumatic SCI Data Sets, including classification of etiology, in a retrospective study involving over 900 patients; only 4% of cases were not able to be classified or were unknown.⁵ Further validation studies using prospective methodology are required. It is anticipated that some revisions of the International Non-traumatic SCI Data Sets may be required following further studies.

Other study design and data collection opportunities. Additional strategies that will improve research in SCDys include increasing the number of multicenter studies involving these patients⁵⁰ and planning studies that involve a larger number of people with SCDys. The range of variables collected in research should be increased, particularly regarding environmental and population characteristics, such as enabling factors and health behaviors, and the way in which health care delivery models influence secondary complications.⁵⁶

Based on recommendation in the International Non-traumatic Spinal Cord Injury Data Sets, the timeframe over which clinical symptoms develop that are attributable to the onset of the SCDys should be coded as acute (≤ 1 day), subacute (> 1 day but ≤ 7 days), prolonged (> 7 days but ≤ 1 month), or lengthy (> 1 month).⁴ The recently published second version of the International Spinal Cord Injury Core Data Set has recommended that in these cases of gradual onset of SCDys, the date of onset of SCDys be taken as the approximate date of the first physician visit for symptoms related to SCDys.³⁷

With increased sample sizes and a better range of variables,⁵⁷ such as the International SCI Data Sets (<http://www.iscos.org.uk/international-sci-data-sets>), to describe patient characteristics, health service use, and outcomes, it will be possible to utilize more advanced statistical methods, such as multivariate regression, to

adjust for confounding variables and computer modeling.^{58,59} In addition, systematic and scoping reviews, along with meta-analyses when sufficient studies are available, can be used to increase the evidence base regarding SCDys.

Other opportunities for SCDys research improvements: funding, preclinical studies, and international research focus

It is important to encourage the funding of research into SCDys. Lack of funding is a major barrier to improving the quality and quantity of SCDys research. The development of other animal models of SCDys, in addition to the models for spinal cord infarction^{60,61} and degenerative spinal conditions,⁶²⁻⁶⁴ and other preclinical research into SCDys is important. SCDys patients should be included in clinical intervention studies in both the acute phase and rehabilitation.

It is suggested that consideration be given to amending the international guidelines for conducting clinical trials in SCI⁵⁴ to include appropriate subgroups of patients with SCDys. For example, patients with SCDys due to progressive etiologies (eg, tumor or multiple sclerosis) would be expected to have major differences in outcomes compared to those with SCI of the same age and should be studied separately, however those with some nonprogressive acquired SCDys etiologies could be included with SCI participants. It is recommended that spinal cord registries (eg, the US Model Systems, Canadian-based Rick Hansen SCI Registry, European Multicentre Spinal Cord Registry) explore ways of including people with SCDys in addition to those with traumatic SCI. Collaborative research networks including SCDys rehabilitation researchers and other national or international groups involved with SCDys should also be explored. One example is spine surgery databases that include patients with cervical myelopathy and pediatric SCI/SCDys, which allow rehabilitation clinicians to implement longitudinal projects that follow children who transition into adult health service.

Conclusions

A more comprehensive understanding of the epidemiology of SCDys is required to better plan health services that can meet the future demand for prevention and rehabilitation of people with spinal cord damage from any cause, including SCDys, and to facilitate optimal rehabilitation and prevention programs.

The increase in scientific publications regarding SCDys over the past 4 decades highlights the importance of this group of heterogeneous conditions to the research community. Our study emphasizes the lack of good quality epidemiological studies regarding incidence, prevalence, and survival in these patients that can serve as a benchmark for guiding future research and informing evidence-based care and policy. Due to the limitations in identifying cases of SCDys and monitoring these over time, health system decision makers are lacking important data for evaluating system performance, whether through prevention, education, or interventions. Without these data and improved research methods, it will be difficult to lobby for additional funding for SCDys research. Major efforts should be made to address the numerous opportunities for improving SCDys research.

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