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REVIEW

Neuropathic pain and spasticity: intricate consequences of spinal cord injury

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Study design: The 2016 International Spinal Cord Society Sir Ludwig Guttmann Lecture.
Objectives: The aim of this review is to identify different symptoms and signs of neuropathic pain and spasticity after spinal cord injury (SCI) and to present different methods of assessing them. The objective is to discuss how a careful characterization of different symptoms and signs, and a better translation of preclinical findings may improve our understanding of the complex and entangled mechanisms of neuropathic pain and spasticity.
Methods: A MEDLINE search was performed using the following terms: 'pain', 'neuropathic', 'spasticity', 'spasms' and 'spinal cord injury'.
Results: This review identified different domains of neuropathic pain and spasticity after SCI and methods to assess them in preclinical and clinical research. Different factors important for pain description include location, onset, pain descriptors and somatosensory function, while muscle tone, spasms, reflexes and clonus are important aspects of spasticity. Similarities and differences between neuropathic pain and spasticity are discussed.
Conclusions: Understanding that neuropathic pain and spasticity are multidimensional consequences of SCI, and a careful examination and characterization of the symptoms and signs, are a prerequisite for understanding the relationship between neuropathic pain and spasticity and the intricate underlying mechanisms.
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INTRODUCTION

This review discusses the need for a phenotype-based classification of both neuropathic pain and spasticity in order to understand the common and diverse mechanisms of these intertwined consequences of SCI.

Following SCI, neuroplasticity, which involves both neuronal, structural and functional responses, is essential for recovery of the neurological function, but the dark side of this neuroplasticity can be the development of neuropathic pain and spasticity.[1] These common disabling conditions negatively affect mood, sleep, quality of life, and participation in activities and active recreation as well as employment.[2–7] Neuropathic pain is present in 50–60% and spasticity in about 70% of individuals living with a SCI.[5,8–11]

Neuropathic pain is a multidimensional constellation of phenomenologically different symptoms and is defined as 'pain caused by a lesion or disease of the somatosensory nervous system'.[12,13] Neuropathic pain following SCI includes at- and below-level SCI neuropathic pain, where at-level pain may consist of both peripheral and central neuropathic pain, while below-level pain is a central neuropathic pain condition.[14] The pain may be spontaneous and described as burning, squeezing, shooting or pricking pain, and/or evoked (allodynia and hyperalgesia), which is most commonly evoked by touch and cold stimuli. Clinically, it may be difficult to distinguish neuropathic pain from other types of pain such as musculoskeletal pain, which is common after SCI, due to, for example, spasms, contractures and overuse.

Spasticity is also a multidimensional constellation of phenomenologically diverse symptoms and has been defined as 'a disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles',[15] and this broad definition of spasticity is adopted in the spinal cord injury musculoskeletal data set.[16] This definition includes velocity-dependent increase in tonic stretch reflexes (muscle tone) and phasic stretch reflexes (exaggerated tendon jerks) that formed the original definition of spasticity,[17] as well as flexor- and extensor spasms, flexor reflexes, and altered motor control. Clinically, it is often difficult to separate spasticity from symptoms and signs caused by structural changes in the muscles.[18]

The aim of this review is to present different domains of neuropathic pain and spasticity with possible different underlying mechanisms and to discuss the assessment of these in preclinical and clinical research. The hope is that a more elaborate classification will improve the translation of preclinical studies to the clinic and understanding of the complex and entangled mechanisms of neuropathic pain and spasticity.

NEUROPATHIC PAIN AND SPASTICITY: TWO SIDES OF THE SAME COIN?

Central neuropathic pain shares many features with spasticity and has even been termed 'sensory spasticity'.[19] Both pain and spasticity can have a late onset and develop slowly over time after SCI, and once developed, they often become chronic. In addition, both conditions

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Table 1 Different domains in neuropathic pain and their assessment in human and animal research

Domain	*Clinical assessment*	*Preclinical assessment*
Ongoing pain	• Numeric rating scale • Visual analog scale	• Conditioned place-preference paradigms
Evoked pain Thermal gain Mechanical gain	Pain intensity to: • Thermal stimulation (for example, thermal rollers, acetone droplet, thermal testing) • Mechanical stimulation (for example monofilaments, cotton, brush)	Supraspinal responses to: • Thermal stimulation (e.g. cold plate, acetone droplet, radiant heat) • Mechanical stimulation (e.g. monofilaments, cotton, brush)
Somatosensory function Thermal loss Mechanical loss	Sensory testing to thermal and mechanical stimuli	Supraspinal responses to thermal and mechanical stimuli
Onset of pain	• Early (within weeks) • Late (within months)	• Early (within days) • Late (within weeks)
Location	Location of pain and sensory loss and gain • At-level • Below-level	Location of sensory loss and gain • At-level • Below-level
Pain quality Burning pain Pressing/squeezing Paroxysmal pain Pricking pain/pins and needles Evoked pain	Pain questionnaires, for example: • Neuropathic pain symptom inventory • Pain Quality Assessment Scale	NA
Other domains Anxiety/depression Pain impact Pain catastrophizing Participation	Questionnaires or interview	Behavioral tests, for example, • Thigmotaxis paradigm • Elevated-plus maze • Burrowing

may be elicited by touch and other non-painful stimulation. Gabapentin and pregabalin, which are classic drugs used in the treatment of neuropathic pain, are suggested also to have an effect on spasticity.[20,21] Similarly, $GABA_A$ receptor agonists, which are sometimes used for spasticity in the form of benzodiazepines, are also suggested to have an effect on central pain and central sensitization, maybe particularly on allodynia and hyperalgesia.[22,23] On the other hand, central pain and spasticity may develop independently, the tricyclic antidepressant amitriptyline, which is also a first-line drug for neuropathic pain,[24] is suggested to increase spasticity,[25] and the most commonly used drug for spasticity, baclofen, has no proven effect in neuropathic pain. So there seem to be both similarities and differences.

It is difficult to examine possible relationships between neuropathic pain and spasticity due to the difficulty in distinguishing neuropathic pain from musculoskeletal pain, which is a very common result of spasticity.[26] Certain pain types are particularly difficult to classify, for example, the characteristic squeezing and pressing type of pain. In addition, the frequent use of drugs for spasticity and pain likely affects the severity of spasticity and pain in individual patients, which may blur a possible correlation between the severity of the untreated symptoms. Furthermore, the failure to differentiate between different phenotypes of pain and spasticity may prevent us from identifying similarities. In a questionnaire study based solely on patient-reported outcomes, the presence of pain was related to the presence of spasticity and a higher intensity rating of muscle stiffness, while only pain with typical neuropathic pain descriptors was related to the frequency of spasms.[5] This suggests that different subtypes of pain and spasticity may be related. The multidimensional nature of pain and spasticity calls for the use of different scales to measure various aspects of spasticity[27,28] and pain,[29,30] and these will be discussed in the following sections.

MULTIDIMENSIONAL ASSESSMENT OF PAIN

For neuropathic pain, there is now good evidence from clinical research to suggest that at-level and below-level pain are two different pain types. Below-level pain often develops months later than at-level pain, and sensory hypersensitivity is a predictor of below-level but not at-level pain.[8,31] However, hypersensitivity is not always present early on in patients who develop below-level pain,[31,32] and within both below-level and at-level pain, there likely are different pain phenotypes with different constellations of sensory descriptors and sensory signs that may reflect different underlying mechanisms and possible different responses to treatment. For example, within both central and peripheral neuropathic pain, five distinct dimensions have been identified based on neuropathic pain descriptors, that is, burning pain, squeezing pain, paroxysmal pain, evoked pain, and pins and needles sensations.[33] Using cluster analysis of the results of quantitative sensory testing, three different clusters have also been identified based on sensory profiles, which are as follows: (1) a cluster characterized by loss of small and large fiber function; (2) a cluster characterized by relatively preserved large and small fiber sensory functions in combination with thermal hyperalgesia and (3) a cluster characterized by thermal sensory loss and mechanical allodynia and hyperalgesia.[34] Psychological factors such as anxiety and depression, pain catastrophizing, and adaptive pain coping are also important factors in the multidimensional neuropathic pain description.[35,36] Evidence is now beginning to emerge supporting that such phenotype-based classifications are related to pain mechanisms and that they may have treatment implications.[29,37] Sodium channel blockers are, for example, suggested to be more effective in patients with preserved pain and thermal sensation than in patients who have mainly sensory loss.[38,39] Some of the factors relevant for characterizing neuropathic pain in clinical research are listed in Table 1 and are also recommended in the International SCI Pain Extended Data Set.[40]

Several SCI models are used in preclinical research, including hemisection, contusion, ischemic and excitotoxic models, but pain assessment remains a challenge. One of the main reasons is the difficulty in assessing the correlate of spontaneous pain, which is the most frequent and troublesome pain symptom in humans.[41,42] Conditioned place-preference paradigms, which are standard preclinical behavioral models used to demonstrate the reward of analgesic drugs, have been used in SCI models.[43] The models are used to assess the presence of tonic pain by, for example, examining the rats' preference for environments that has previously been paired with analgesics or not. Burrowing, which is an ethologically relevant rodent behavior, has recently been used as an indication of behavioral dysfunction and has shown some degree of predictive validity as an outcome measure for pain.[44] Psychological domains can also be assessed using, for example, the thigmotaxis paradigm in the open-field test, the elevated plus maze for assessment of anxiety-like behavior, or the forced swimming test for depression-like behavior.[45] Like in humans, evoked responses to pinprick, dynamic

Table 2 Different domains of spasticity and their assessment in human and animal research

Domain	*Clinical assessment*	*Preclinical assessment*
Muscle spasms	• Penn Spasm Frequency Scale • Spasm frequency score • Spasm severity scale • The Spinal Cord Assessment • Tool for Spastic Reflexes	• Twitches • Frequency and severity of spasms e.g. during swimming • Withdrawal reflexes to mechanical or thermal stimuli • EMG during withdrawal
Velocity-dependent increase in resistance to passive movement	• Intensity rating of muscle stiffness • Ashworth scale • Modified ashworth scale • Modified tardieu scale • EMG activity to stretch • Wartenberg pendulum test	• Velocity-dependent changes in resistance during flexion • Tail resistance to stretch • EMG activity to stretch
Increased tendon reflexes	• Deep tendon reflexes • T-reflex	• T-reflex
Clonus	• Clonus score • The Spinal Cord Assessment • Tool for Spastic Reflexes	• Quantification of repeated muscle jerks e.g. of the tail or during onset of stance
Dyssynergic pattern of co-contraction during walking	• Gait and movement analyses	• Dynamic electromyograms • Assessment of movements

stimulation using a brush, and cold stimuli using acetone droplets, or thermally regulated plates can be assessed,[46,47] but the assessment of stimulus-evoked pain-like behavior poses specific problems in models of central pain. These often rely on simple spinally mediated withdrawal reflexes, which are present after spinal transection and may be increased as part of the development of spasticity. It has been shown that motor and projection neurons in the pain pathways are affected differently by SCI and that withdrawal reflexes do not always reflect pain-like hypersensitivity.[41,46,48–50] Methods that depend on cortical processing such as operant escape testing and the place escape/avoidance paradigm or at least are dependent on the brain stem (for example, licking, guarding and vocalizing) are needed, but it is important to keep in mind that the neural circuits subserving vocalization reflexes and conscious appreciation of nociceptive intensity also can react differently to SCI.[46–48,50] Examples of assessment methods of different neuropathic pain subtypes in preclinical research are listed in Table 1.

MULTIDIMENSIONAL ASSESSMENT OF SPASTICITY

The multidimensional nature of spasticity with various distinct presentations also calls for the use of different instruments to measure the various clinical presentations.[27,28,51] The different components of spasticity are likely to have different underlying mechanisms. For example, increased muscle tone and exaggerated tendon reflexes can occur after central nervous system lesions at all levels, while exaggerated flexion and withdrawal reflexes are seen after spinal lesions, and modulatory effects of descending reticulospinal pathways in the dorsolateral column can have opposite effects on stretch and flexion reflexes.[52]

The most commonly used clinical instruments to measure muscle tone are the Ashworth Scale,[53] the Modified Ashworth Scale[54] and the Modified Tardieu Scale.[55] Spasm scales include the Penn Spasm Frequency Scale[56] and the spasm frequency score.[27] The Spinal Cord Assessment Tool for Spastic Reflexes evaluates three distinct types of motor behavior: clonus, flexor spasms and extensor spasms.[57] Clonus in response to a rapid passive dorsiflexion of the ankle is rated based on the time clonus is maintained, severity of flexor spasms is rated based on the response to a pinprick stimulus applied to the plantar foot, and extensor spasms based on the duration of visible muscle contractions to hip and knee extension.[57] Electrophysiological measures include electromyography (EMG) responses to electrical stimuli such as the Hoffmann reflex (H-reflex), the F-wave, the flexor reflex or tendon percussion (the tendon reflex, T-reflex), but they do not directly correlate with clinical signs.[58] In addition, different gait and movement analyses can be made. The different modalities of spasticity and examples of assessment methods are presented in Table 2.

Similar to the situation with pain, it is challenging to assess the different types of spastic motor behaviors in rodents (Table 2).[59] Different methods have been developed to assess muscle resistance to stretch at different velocities in the limb or tail, including a computer-controlled ankle rotational system,[60] a handheld strain gauge,[61] a digital resistance transducer[62] and measurement of EMG responses. As mentioned above, stimulus-evoked paw withdrawal thresholds do not correlate with hypersensitivity, but they also do not seem to correlate with increased muscle tone, and are suggested to reflect hyperreflexia with pathophysiological analogs of spasms or clonus.[50] The evaluation of stimulus-evoked paw withdrawal can be compared to the evaluation of flexor spasms in the Spinal Cord Assessment Tool for Spastic Reflexes. Similarly, tail flick to pinch or radiant heat can be used for evaluation of withdrawal tresholds.[63] Quantitative and qualitative assessment of hindlimb and tail spasms during swimming has also been used to assess spasms.[64] Co-contraction patterns of antagonistic muscles can be assessed using, for example, dynamic electromyograms of muscle contractions during bipedal gait,[61] and detailed analysis of joint movements may identify various signs of spasticity.[65]

IDENTIFYING MECHANISMS THAT NEUROPATHIC PAIN AND SPASTICITY HAVE IN COMMON

Neuropathic pain and spasticity are not caused by simple mechanisms, but involve a complex chain of alterations in various interdependent networks.[18,66,67] Proposed mechanisms of both neuropathic pain and spasticity involve disinhibition from loss of descending pathways or interneurons, neuronal hyperexcitability, ectopic firing, sprouting, receptor upregulation, deafferentation effects on rostral or caudal neurons, glia activation and neuroinflammation, although the neuronal circuits involved in neuropathic pain and spasticity are likely to differ—at least to some extent.[60,67] The multidimensional nature of neuropathic pain and spasticity is important to consider when studying the underlying mechanisms or assessing treatment effects in both preclinical and clinical research, since the different symptoms and signs of neuropathic pain and spasticity can exist independently and do not necessarily have common underlying mechanisms or treatment responses.[18,29]

Most clinical and preclinical research has focused on either pain or spasticity, while few studies have investigated both conditions at the same time. One exception is a series of studies carried out by

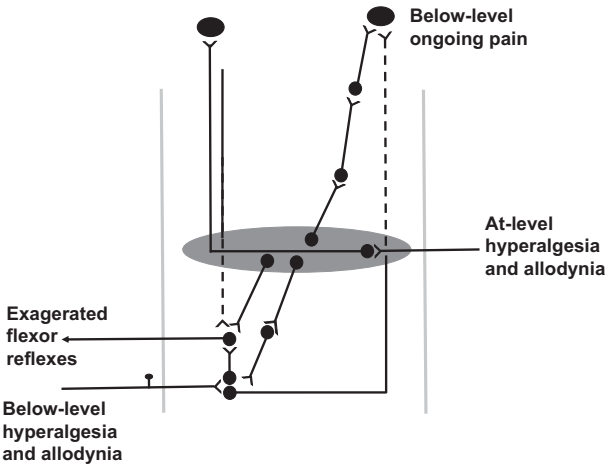

Figure 1 A simplified schematic representation of how lesions and hyperexcitability in different pathways may be involved in generating various symptoms and signs of neuropathic pain and spasticity. The grey lines indicate the spinal cord, the dark grey area the injury site, and the dashed lines interrupted axons. For details, please see the text. Adapted from Vierck *et al.*[52]

Vierck and colleagues more than 15 years ago. On the basis of extensive animal studies,[68,69] they suggested that exaggerated flexion and withdrawal reflexes as well as below-level pain result from a combination of long tract damage and abnormal activity in the spinal grey matter as well as a facilitatory role of propriospinal systems, albeit with different circuits involved (Figure 1).[52] In this model, exaggerated withdrawal reflexes result from disrupted descending reticulospinal pathways and spread of neuronal hyperexcitability to motoneurons, whereas allodynia and hyperalgesia and possibly also ongoing below-level pain are suggested to result from facilitatory effects on partially preserved spinothalamic tract neurons. Ongoing below-level pain in patients with a complete lesion is proposed to involve effects on deafferented supraspinal neurons in the pain pathways. This theory is supported by studies finding a correlation between evoked at-level pain and ongoing below-level pain.[70–72] Further studies that carefully assess various symptoms of SCI and their changes over time and a better understanding of the translation of behavioral correlates of pain and spasticity from animals to humans and back are needed in order to further understand how various changes in interdependent neuronal networks can result in different symptoms and signs.

CONCLUSIONS

Neuropathic pain and spasticity are multifactorial and complex consequences of maladaptive neuronal plasticity after SCI. It is important to distinguish between various symptoms and signs in order to understand the relationship between neuropathic pain and spasticity. Different constellations of pain and spasticity, and injury characteristics (for example, at- and below-level pain, ongoing and evoked pain, shooting and burning pain, spasms and increased muscle tone, complete and incomplete lesions) may reflect different underlying mechanisms. Unraveling the complex constellations, differences, and similarities of these different symptoms and signs is important for increasing our understanding of the intertwined mechanisms. We also need a better understanding of the predictability of outcomes in animal models to model human pain to improve the translation of preclinical trials. These are immense tasks for the future but with significant importance for understanding mechanisms and developing new and differentiated treatments.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

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