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Phenotypes and Predictors of Pain Following Traumatic Spinal Cord Injury: A Prospective Study

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Abstract: Pain is a serious consequence of spinal cord injury (SCI). Our aim was to investigate the temporal aspects of different types of pain following traumatic SCI and to determine possible predictors of neuropathic pain. Prospective data on 90 patients were collected at 1, 6, and 12 months after traumatic SCI. The patients completed questionnaires on pain severity, descriptors, and impact and underwent clinical examination with bedside sensory testing. Eighty-eight patients completed the 12-month follow-up. Approximately 80% of patients reported any type of pain at all 3 time points. Neuropathic pain related to SCI increased over time, and musculoskeletal pain decreased slightly, with both being present in 59% of patients at 12 months; other neuropathic pain not related to SCI and visceral pain were present in 1 to 3%. At-level neuropathic pain present at 1 month resolved in 45% and below-level pain resolved in 33%. Early (1 month) sensory hypersensitivity (particularly cold-evoked dysesthesia) was a predictor for the development of below-level, but not at-level, SCI pain at 12 months. In conclusion, the present study demonstrates phenotypical differences between at-level and below-level SCI pain, which is important for future studies aiming to uncover underlying pain mechanisms.

***Perspective:** The finding that early sensory hypersensitivity predicts later onset of below-level central neuropathic pain may help to identify patients at risk of developing neuropathic pain conditions after traumatic spinal cord injury. Information about onset of pain may help to identify different phenotypes in neuropathic pain conditions.*

***Key words:** Spinal cord injury, neuropathic pain, allodynia, central pain, sensory processing.*

Pain is a common and sometimes severe complication of spinal cord injury (SCI).[8] The new International Spinal Cord Injury Pain Classification (ISCIP)[4] represents a tool to divide SCI pain into different categories and a way to study potential underlying mechanisms and risk factors. According to the ISCIP, the first tier divides pain according to the type, that is, nociceptive, neuropathic, and other pain. Neuropathic pain, which is pain caused by a lesion or disease of the somatosensory nervous system,[12] is further divided into SCI-related neuropathic pain and other neuropathic pain. SCI neuropathic pain is further divided into at-level and below-level SCI pain. At-level pain is defined as neuropathic pain located within the dermatome at and 3 dermatomes below the neurological level, except for SCI pain in context with cauda equina lesions, which is always at-level pain. Below-level pain is defined as neuropathic pain that is present more than 3 dermatomes below the neurological level and may extend to the at-level region.

Neuropathic pain is caused by a complex combination of different pathophysiological mechanisms, which are thought to manifest as different pain phenotypes, that is, different constellations of a patient's pain such as its

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descriptors, temporal aspects, or sensory manifestations. It is hoped that identification of different phenotypes will increase the ability to uncover specific underlying mechanisms, thereby improving personalized pain treatment.[20] A prospective study from 2003 suggested that at-level and below-level SCI pain may be 2 distinct types of neuropathic pain based on the time of onset, but the mechanisms for these are still unclear.[16]

Little is known about predictors of SCI neuropathic pain. Sensory hypersensitivity is common and indicates that central neuronal hyperexcitability is present.[10] Allodynia often has an early onset,[17] which suggests that sensory hypersensitivity might be a predictor for the later development of neuropathic pain. A recent study of 28 patients with SCI showed that those who later developed below-level central pain had higher rates of mechanical allodynia and hyperpathia in the first months following SCI.[23]

The aim of the present prospective study was 2-fold: 1) to identify pain phenotypes through a detailed analysis of pain characteristics observed over the first year following traumatic SCI and 2) to determine if sensory hypersensitivity, as assessed by bedside sensory testing, predicts the development of at-level and below-level SCI neuropathic pain at 12 months.

Methods

Patient Recruitment

Patients with traumatic SCI aged ≥18 years admitted consecutively to the Department of Neurosurgery, Aarhus University Hospital, Denmark, and to the Department of Neurology, Karolinska University Hospital, Stockholm, Sweden, were included. Exclusion criteria were alcohol or substance abuse; psychiatric disease; and inability to participate because of, for example, severe brain damage, language problems, dementia, or other clinical conditions. Patients were examined within 1 month of SCI (n = 38) if the clinical condition allowed, otherwise within a maximum of 3 months (n = 52) and with follow-up visits at 6 (n = 78) and 12 months (n = 88). A telephone interview was used if a physical visit was not feasible. The study was approved by the respective local ethical committees (Regionala etikprövningsnämnden Stockholm no. 2007/1558-32 with amendment 1843-32 and the National Committee on Health Research Ethics for Central Region Denmark no. M-20070090) and the Danish Data Protection Agency, Copenhagen, Denmark (no. 2007-41-0605). All patients gave informed written consent.

Procedure

At first examination, the etiology of SCI was classified using the International Spinal Cord Injury Core Data Set,[6] and patients were asked about preexisting chronic pain defined as pain present at least once a week for at least 3 months before the SCI. At all visits, spinal lesions were classified according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI).[13] Patients were interviewed about the presence of abnormal sensations: paresthesia (abnormal sensations, whether spontaneous or evoked, that are not unpleasant) and dysesthesia (nonpainful abnormal sensations, whether spontaneous or evoked, that are unpleasant) classified as warm, cold, pressing, tingling, or other sensations and any pain present within the last 7 days. Pain was classified according to the ISCIP at the time of visit/telephone contact.[4] Neuropathic pain should fulfill the criteria for definite neuropathic pain[19] and not be primarily related to movement, inflammation, or other local tissue damage. Neuropathic pain was divided into pain occurring as a consequence of SCI (at-level and below-level pain) and other neuropathic pain. For each pain type (at-level and below-level SCI neuropathic pain, other neuropathic pain, musculoskeletal pain, and visceral pain), patients completed the short-form McGill Pain Questionnaire,[15] and the examiner completed the International Spinal Cord Injury Pain Basic Data Set, which includes information about location, average pain intensity (numeric rating scale [NRS], 0-10), onset of pain, number of days with pain during the past week, and duration of pain.[22] For overall pain, patients completed the Brief Pain Inventory and the Pain Interference scale,[5] and pain treatment was recorded from medical record and by asking the patient what pharmacologic and nonpharmacologic treatment he or she was taking/using for pain relief.

At all visits, a bedside sensory testing was performed above, at, and below injury level. Pain and unpleasantness to brush (Somedic AB, Hörby, Sweden), single pinprick (evoked by bending a Semmes-Weinstein monofilament, no. 5.88, bending force 75.9 g/745 mN; Semmes-Weinstein, Stoelting, IL), cold and warm stimuli using a thermal roll of 20 and 40°C (Somedic AB), and repetitive pinprick (evoked by applying the monofilament repetitively with 2 Hz for 30 seconds) were assessed using an NRS (0–10). First, the areas at and below injury level were roughly screened with a brush and a cold thermal roll. In case of hypersensitivity, the area with maximal pain/unpleasantness was assessed. In case of no hypersensitivity, for examining the at-level area, an area clearly within the at-level area was chosen without specific criteria, and for examining the below-level area, the calf was used (patients with cauda equina were only assessed at level). The right facial cheek was used as above-level reference. The intensity ratings obtained at and below injury level were subtracted with the value from the cheek, and this value was used. Any value for pain or unpleasantness (dysesthesia) above 0 (when subtracting the value from the cheek area) was considered to represent hypersensitivity to the given modality (brush, cold, warm, single, and repetitive pinprick). All examinations and diagnoses were done by L.W., K.T., or C.N. in Sweden and by N.B.F. in Denmark using the same equipment and following a standardized protocol after training and video recording.

Statistical Analysis

The statistical analyses were carried out in SPSS, version 13 (SPSS Inc, Chicago, IL). Baseline data were described by mean and standard deviation (SD) if