

Review

Pain and rehabilitation after spinal cord injury: the case of sensory spasticity?

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Abstract

Sixty percent of patients with posttraumatic para- or tetraplegia suffer from severe, continuous burning and/or lancinating pain. Multiple sclerosis produces pain in more than 30%. This pain can be as important as the absent mobility or sexual function as a cause of lowered quality of life. Two unique types of longstanding neuropathic pain can be recognized in persons with spinal cord injury: (1) segmentally distributed pain at the lesion; and (2) pain in the body below the lesion, often with late onset. The first type could be produced by nerve root entrapment or by direct segmental deafferentation. The second type probably contains several forms of central pain, evoked either by the original spinal lesion, by an expanding syrinx in the spinal cord or by secondary changes at higher levels of the somatosensory systems. Patients with central pain almost always have stimulus-independent pain. Its intensity may vary independently, be related to the presence of visceral activity/inflammation or be constant. In addition, stimulus-dependent pain is sometimes present, usually because skin areas or viscera below the lesion are allodynic. Partial spinal lesions, especially centrally in the cervical spinal cord, may be more prone to produce pain than are complete lesions. There is limited analgesic effectiveness in controlled studies of serotonin reuptake inhibitors, of sodium channel blockers (lidocaine, tetracaine), of the GABA receptor agonist baclofen (one study) and of the NMDA-receptor antagonist ketamine (one study). There are anecdotal reports on oral carbamazepine, on gabapentin, on intrathecal opiates and also on the α_2 -agonist clonidine, being effective in central neuropathic pain. Neurostimulation is effective only if it evokes paraesthesia in the painful area; hence TENS may give relief of segmental pain. Neurodestructive procedures and central neurostimulation have been largely unsuccessful. As in other longstanding pain, improved coping through cognitive-behavioural rehabilitation may be helpful for the clinical outcome.

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1. Introduction

Injury to the human spinal cord has a variety of causes. The most common cause is mechanical trauma, with a

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spectrum of culturally derived accidents, such as crashing a motorbike, diving in shallow waters, playing violent sports (notably rugby), being the victim of criminal acts (stabbing, low velocity gunshot wounds) or of occupational injuries, mostly in the construction industry [15]. Common to the traumatic cases is that young men are usually the victims, leading over females by at least 4 to 1 [14]. Spinal cord injury can also be caused by inflammatory or degenerative processes such as in multiple sclerosis or in tuberculoma of the spinal cord, which can occur in all ages, most commonly from young adult age up. Later in life, ischemic spinal cord injury may result from occlusion of arterial branches due to thrombosis or to dissecting vascular phenomena. The incidence of traumatic spinal cord injury in the western world is usually considered to be one to two cases per 100 000 inhabitants per year. The highly specialized care for these patients has dramatically improved the life expectancy; prior to the introduction of specialized care during the late 1950s, life expectancy in Scandinavia was 1.5–2 years, whereas now persons with paraplegia have almost the same life expectancy as the general population while those with tetraplegia seem to live 10–20 years less [49]. The dramatic improvement is due to developing specialized spinal cord injury units during and after the second world war, notably in the UK (Sir Ludvig Guttsman in Stoke-Mandeville and others; see Ref. [3]). The experiences from these centers were rapidly disseminated to the rest of Europe, United States and Australia and, by the early 1960s, specialized spinal cord injury units had been established in most industrialized countries.

2. Postacute spinal cord injury rehabilitation

Many general physicians would perhaps think that the first shock striking the spinal cord injury victim is the spinal shock, as known from the classical physiology of Sherrington. However, the greatest shock is certainly that from the lost bodily identity by the spinal cord injured patient who suddenly realises that he or she has suddenly lost his or her ambulatory capacity along with many other important bodily functions.

In the early rehabilitation of these patients focus is on vital functions, providing adequate respiratory care, thrombosis and decubitus prophylaxis as well as an adequate urinary bladder management. Simultaneously, specially trained staff provide crisis psychotherapy, much needed for a spinal cord injured person to be able to gradually reflect over his or her new situation. In this work, an early contact with an independent person who has him- or herself experienced disability from spinal cord injury is of utmost importance. In most rehabilitation programs this is achieved within the first week and is usually considered extremely valuable by the newly injured patient [3,21].

An important part of the physical rehabilitation program

is to enable the patient to resume upright posture, a process that may be slowed by the lack of stability of the vertebral fractures, nowadays usually treated by fusion surgery. Another problem is posed by orthostatic reactions due to insufficient autonomic control. This requires gradual exposure to more and more upright body position and, sometimes, treatment with α -adrenergic medication is needed. Obviously prophylaxis and treatment of contractures in major joints are likewise of great importance. When the patient has regained upright posture, the training of equilibrium and muscle strength becomes important, as does fitness training, for example with an arm ergometer. The next step is to train in transferring from bed to chair to vehicle and to practice wheelchair skills both in a manual chair and, if high injuries, in an electric wheelchair.

Then comes resumption of activities of daily living, focusing on personal hygiene, dressing and other aspects of personal care. Other components in the program include uroprophylaxis and adjusting to the most efficient way of regular urinary bladder emptying, nowadays usually clean intermittent catheterization. Likewise, it is sometimes necessary to adjust to the autonomic dysfunction due to the lack of central nervous system control of the autonomic outflow. For example, if the T2–3 segments are intact, the control of heart rate is normal and with the T6 segment intact, the person has also autonomic control of the large vessels preventing hypotensive reactions. Some patients may experience attacks of autonomic dysreflexia, for example due to gastrointestinal problems, with sudden hypertension that gives a definite risk for cerebrovascular lesions. In addition, body temperature regulation in high injuries may require special attention.

In later stages of the post-acute rehabilitation, counselling on relations, on sexual activity and on the fertility issue, where the now considerable possibilities of fertilization and childbirth are important matters to inform about and to discuss.

Adjustment of living quarters as well as providing the spinal cord injured person with a car to provide autonomy (today possible from lesions at the C5–6 level and down) are likewise important components, as are testing suitable technical aids, both of low and high tech character. At the same time, planning of future education and resuming work are important issues to bring up and to support. Usually, persons with spinal cord injury maintain annual or biannual contact with the rehabilitation team for the rest of their lives. The end goal for the rehabilitation process is to enable the fullest range of activities and active participation in all aspects of human life.

3. Spinal cord injury pain

A gradually emerging issue in spinal cord injury care is that of chronic pain. A suitable taxonomy has been lacking in this field until recently, when the International Associa-

Table 1
Proposed classification of pain related to spinal cord injury (adapted from IASP Taskforce on SCI Pain [38])

| Broad type (Tier 1) | Broad system (Tier 2) | Specific structures/pathology (Tier 3) |
|---------------------|-----------------------|---|
| Nociceptive | Musculoskeletal | Bone, joint, muscle trauma or inflammation Mechanical instability Muscle spasm Secondary overuse syndromes |
| | Visceral | Renal calculus, bowel, or sphincter dysfunction, etc. Dysreflexic headache |
| Neuropathic | Above level | Compressive mononeuropathies Complex regional pain syndromes |
| | At level | Nerve root compression (including cauda equina) Syringomyelia Spinal cord trauma/ischemia (transitional zone, etc.) Dual level cord and root trauma (double lesion syndrome) |
| | Below level | Spinal cord trauma/ischemia (central dysesthesia syndrome, etc.) |

tion for the Study of Pain Taskforce on Spinal Cord Injury Pain published a key paper [38] (cf. Ref. [36]). Here, a classification is proposed in three tiers (Table 1). The first tier classifies the pain condition into either nociceptive or neuropathic, notions uniformly agreed upon in the main taxonomy of pain syndromes published by the IASP [30]. The second tier provides further definition of these broad pain types and provides further direction to treatment. Nociceptive pain is divided into musculoskeletal and visceral pain types and neuropathic pain is divided into above injury level (with relation to the life situation of the spinal cord injured), at injury level (located in a segmental pattern at the level of injury) and below injury level (located diffusely below the level of injury). The third tier indicates the specific pathology and all structures involved. In this third tier, many of the specific pathologies are still unknown and can only be speculated about. However, it is of outmost importance for further clinical research in the field that a uniform taxonomy is established.

Below level spinal cord injury pain was described first by Guillian and Garcia in 1931 and by Riddoch [33]. However, already in 1912 Spiller and Martin [41] performed the first cordotomy in a patient with pain due to a spinal tuberculoma, which is probably the first documented observation of a spinal cord injury pain.

3.1. Epidemiology of spinal cord injury pain

In several cross-sectional studies the prevalence of pain amounts to 60–70% [8,34]. The pain is usually rated as severe in 20–40% of cases. Recently, a longitudinal study of 100 consecutive newly injured patients followed for 6

months showed that 64 of them had pain during this time period: 40% had musculoskeletal pain; 36% had at level neuropathic pain and 19% had below level neuropathic pain, usually of severe intensity [37]. The same authors could also demonstrate an interesting difference in temporal patterns between the various forms of pain reported. Musculoskeletal pain patterns and at level neuropathic pain were most common in the early stages of spinal cord injury, whereas below level neuropathic pain was the dominating and remaining pain condition 3–6 months after injury with a prevalence of around 20% of the cases. Turner and Cardenas [44] found 64% of responders to a mailing list to spinal cord injury patients to have below level pain. In a large questionnaire study Störmer and co-workers [42] found that more than a third of the below level spinal cord injury pains began more than a year after the injury and 30% more than 10 years after the injury. Similarly, multiple sclerosis patients report chronic lower body/leg pain of central origin in one-third of cases [5].

As regards location of the spinal cord injury, at level neuropathic pain is most common in hemicord injuries and lacking in anterior cord injuries. In the latter type of injury, below level neuropathic pain seems the most common [37]. Pain may adversely influence the self-assessed health status [34], and can also maintain high stress levels [42] as well as limit activities of daily living and, therefore, restrict participation and quality of life [46]. Some patients are even willing to trade loss of recovery for pain relief [31] even if this is not evident in a more recent study [47]. The present discussion will focus on those pain conditions, dominating the chronic life situation of the spinal cord injured and also those most difficult to treat, the at level and below level neuropathic pain conditions (cf. Ref. [32]).

3.2. At injury level neuropathic pain

Pain conditions at level of the spinal cord injury are usually considered to be one of two types. In the first type, the patient usually experiences a lancinating, stabbing pain in the nerve root distribution from the time of injury. The pain condition is thought to occur from nerve root entrapment and may occasionally benefit from decompression. The second type of at level neuropathic pain is experienced as a girdle pain uni- or bilaterally in two to four segments of the transitional region. The pain is stimulus independent and often accompanied by troublesome allodynia or hyperalgesia. This bilateral pain is thought to arise from segmental deafferentation. In Störmer's and co-workers investigation, 17% of 591 patients experienced at level neuropathic pain only [42].

3.3. Below injury level neuropathic pain

Below level neuropathic pain is usually denoted the central dysesthesia syndrome and is characterized by stimulus-independent burning, continuous pain [13]. Often complete anesthesia is present in the painful body parts, but sometimes mechanical and/or thermal allodynia can be observed. The prevalence in 591 SCI pain patients was for below level pain 47% and for below and at level pain 22% [42]. Incomplete injuries seem to be over-represented [25].

At times, the dorsal spinal pathways are partially preserved [6] which is interesting in conjunction with the

experimental finding that in the lightly anesthetized rat, nociceptive transmission is present in all spinal funiculi except the ventral ones [26]. It is reasonable to assume that central spinal pain may have a variety of causes, which is also mirrored by the fact that the few therapeutic agents available are occasionally, not regularly, effective. One obvious possibility is that such pain is due to processes in sensory systems equivalent to those causing spasticity in motor systems (cf., e.g., Ref. [1]). From experimental studies, it is known that sensory projection neurones and segmental reflex pathways may share interneurons (e.g., Ref. [35]). Hence, the term *sensory spasticity* might give food for thought. In a sense, the situation may be similar to that in limb phantom pain [29]. One recent but small human study points to a role for NMDA receptors in central dysesthetic pain of spinal origin [17].

3.4. Pharmacotherapy

Based on anecdotal evidence, amitriptyline, mexilitene, clonidine, gabapentin and lamotrigin are often tried in below level neuropathic pain. Recently, intrathecal infusion of opiates, sometimes mixed with local anesthetic solution has been advocated. However, to date only eight randomized controlled trials of pharmacological therapy in at and below level neuropathic pain have been published (see Table 2). It can be seen that there is limited analgesic effectiveness in controlled studies of serotonin reuptake inhibitors, of sodium channel blockers intrathec-

Table 2
RCTs of pharmacotherapy (modified from Ref. [20])

| Trial (irst author) | Pain type | Sample (n) | Drug | Duration | Outcome |
|---------------------|---|------------|------------------------------------|--------------------------------------|--|
| Davidoff [12] | At or below level neuro-pathic | 18 | Trazodone HCl 150 mg | 8 weeks | Trazodone = placebo |
| Loubser [27] | At or below level neuro-pathic | 21 | Lidocaine i.th. 50–100 mg | Two injections, 1 h apart | Lidocaine > placebo |
| Herman [24] | Below level neuropathic and spasm-related | 7 | Baclofen i.th. 150 µg | Two infusions on successive days | Baclofen > placebo |
| Drewes [16] | At or below level neuro-pathic | 20 | Valproate 600–2400 mg | 2×3 weeks, 2 weeks washout | Valproate = placebo |
| Eide [17] | At or below level neuro-pathic | 9 | Ketamine i.v. or Alfentanil i.v. | Three infusions, 2 h apart | Ket > placebo Alf > placebo Ket = Alf |
| Chiou-Tan [9] | At or below level neuro-pathic | 11 | Mexiletene 450 mg | 2×4 weeks, 1 week washout | Mexiletene = placebo |
| Attal [2] | At or below level neuro-pathic | 10 | Lidocaine i.v. 5 mg/kg | 2×30 min, 3 weeks apart | Lidocaine > placebo |
| Siddall [39] | At or below level neuro-pathic | 15 | Morphine i.th. and Clonidine i.th. | Minimum four injections, 1 day apart | Mor = placebo Clon = placebo Mor/clon > plac |

ally (lidocaine, tetracaine), of the GABA receptor agonist baclofen (one study) and of the NMDA receptor antagonist ketamine or of the opioid alfentanil intravenously. All studies suffer from small numbers of patients, with a substantial risk of type two statistical errors. In addition, none of them distinguish between below level and at level neuropathic pains, although they most probably are due to different mechanisms.

3.5. Physical therapies

Only open studies of nonpharmacological therapies have been published. A special case relates to surgical treatment of posttraumatic cysts (syringomyelia) in the spinal cord, which can be very successful, not only to halt neurological progress but also for the alleviation of pain [18]. As regards cordotomy (see Ref. [40]), one study claims that 15 out of 25 patients have experienced temporary relief, whereas the results of cordectomy in paraplegic pain are contradictory in that one study claims 14 out of 15 improved if the cordectomy was below Th11. Another study, however, finds no effect in five cases of this procedure [29]. Tasker et al. [43] report that intermittent, shooting pain may be more effectively relieved by destructive surgery than continuous burning pain. Dorsal root and dorsal root entry zone lesions with electrocoagulation have been effective in some studies on at level neuropathic pain and by one group also in below level pain if the lesions are extended to 'hyperactive' areas, as defined by mass recording. As regards stimulation techniques, transcutaneous electrical nerve stimulation has been found effective on at level neuropathic pain in a minority of cases [40], whereas spinal cord stimulation and stimulation at thalamic or frontal cortical levels have gained only anecdotal support.

3.6. Considerations

As with all chronic pain conditions, the first line of therapy after a thorough assessment [7] is information. Regarding specific analgesic therapy, the situation today, 90 years after the first cordotomy for central pain is in most cases still very difficult. If amitriptylin and gabapentin (as well as some of the other new antiepileptic medications, tried ad libitum) do not produce relief, one often has to resort to intrathecal infusions of morphine/lidocain/clonidine alone or in mixture that at best produces partial pain relief and with a considerable resource consumption (cf. Ref. [19]). In addition, improved coping through cognitive-behavioural rehabilitation may be helpful for the clinical outcome (cf. Ref. [28]). It is therefore vital that our understanding of the underlying mechanisms increase, so that more efficient therapies become available. One important step in this direction is to develop relevant animal models of spinal cord injury pain [48].

4. Possible relevance of animal models for spinal cord injury pain

Four models of spinal cord injury pain have so far been devised. One is an ischemic spinal cord injury described in 1991 by Hao and co-workers [22,23]. This rat model is based on intravenous injection of a dye and laser irradiation on the exposed spinal cord, producing a partially ischemic thoracic lesion with at injury level mechanical and cold allodynia. The authors has found that the symptoms can be blocked initially by lidocaine, mexilitene and tocainamide and that the late mechanical allodynia is blocked by the NMDA blocking agents MK 801, CGS 19755 and dextrometorphan. They have also demonstrated that implantation of spinal chromaffin cells decreases the allodynia.

Another model is the excitotoxic spinal cord injury published by Yeziarski et al. [50]. This injury gives cavitation neuronal loss and inflammation at the site of injury and excessive grooming by the experimental animals at the level of injury bilaterally. A thermal hyperalgesia and mechanical allodynia has been demonstrated in the hindpaws. Spinal chromaffin cell transplantation seems to decrease overgrooming.

The third model is the hemisection spinal cord injury published by Christensen and Hulsebosch in 1996 [4,10,11]. This model is based on hemisection at the TH13 level and produces stable allodynia for 10–160 days, unfortunately both above and below the lesion. The injection of NMDA or AMPA blockers alleviates the mechanical allodynia.

The fourth model is the anterolateral cordotomy spinal cord injury recently published by Vierck and co-workers [45,48], where the procedure creates allodynia and hyperalgesia as well as caudally directed overgrooming, proceeding to autotomy. Abnormal resting and evoked activity can be recorded in the ventral basal thalamus of this model.

It can be safely said that only the fourth of these four models may represent below injury level pain and that much work remains before the relevant pain-generating mechanisms are defined. Only then can effective therapy be developed.

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