Pain Associated with Spinal Cord Injury: Mechanisms and Treatment

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A major problem of studies with spinal cord injury (SCI) pain has been the lack of consistent terminology. Thus, in 1997 our SCI research group proposed a much simplified and, we hope, more logical classification of pain after SCI (1). We also suggested a broad framework that could guide mechanistic studies of SCI pain, acknowledging that as late as the mid-1990s, there was little in the way of definitive evidence to indicate which mechanisms were indeed of significance for clinical management (2,3). Subsequently the IASP set up a Task Force on SCI Pain (4).

A major hurdle in the study of SCI pain was the almost complete absence of a valid animal model. In view of the key role of trauma, we developed a rat SCI model that depended on a consistent contusive injury to the spinal cord (5). This model has served as the basis for much further research in this area. Other models have been developed based on excitotoxic lesions or ischemic lesions (6). The availability of a range of animal models is important in view of the multitude of causes of SCI, including trauma, infection, hematoma, cancer, ischemia, neurotoxicity, and multiple sclerosis. Sadly some of these causes are associated with treatment methods used for acute, chronic, and cancer pain.

SCI Pain: Types and Prevalence

Another major deficit in the knowledge base of SCI pain was the great inconsistencies in published work concerning the prevalence of different types of pain after SCI. Thus, we embarked on a study that provided an accurate description of SCI pain from the early postinjury phase up to 6 mo after the injury (7) and then extended to 5 yr after SCI (8,9). These studies used the nomenclature suggested in the original taxonomy article, namely "musculoskeletal pain," "at-level neuropathic pain," "below-level neuropathic pain," and "visceral pain." An important finding in this study was that 50% of patients had neuropathic pain in the early postinjury phase and this percentage remained consistent to 6 mo. Our 5-yr follow-up study confirms that neuropathic pain remains a persistent major problem in patients with SCI. An important side issue is the recognition that a significant number of patients have nonpainful sensory phenomena after SCI (8,9). Another interesting yield from our studies is the finding that patients who have surgery in association with SCI have the same incidence and types of post-SCI pain as do patients who do not have surgery (10); the only influence of surgery was an increased incidence of musculoskeletal pain in the first 2 wk after SCI (and surgery) (10).

The 5-yr follow-up study (9) found the following prevalences at 5 yr after SCI: musculoskeletal pain, 59%; at-level neuropathic pain, 41%; below-level neuropathic pain, 34%; and visceral pain, 5%. In the cases of at-level neuropathic pain and below-level neuropathic pain there were strong correlations with the presence of these pain types at all earlier time points. Thus it would appear that patients who develop these problems are likely to continue to have them for a long period of time, or even permanently.

SCI Pain Types/Characteristics and Some Specific Treatments

In addition to the four major types of SCI pain noted above, there are a number of other pain types, some of which fall within these major categories that are of clinical significance and may warrant a particular strategy of treatment.

Musculo-Skeletal Pain

Mechanical Spinal Instability

This type of pain is more likely to be present immediately after spinal injury and, if severe, will require surgical correction. The characteristics of this type of pain are as follows:

- Disruption of ligaments/joints or fracture of bone.
- Early onset of pain ± "somatic referral."
- Movement in abnormal planes/ranges.
- Position related, increased by activity, decreased by rest.

Diagnosis of this type of pain requires flexion and extension views on plain radiographs complemented

where required by CT and/or MRI scanning. In minor cases of instability, the pain may be managed by a combination of nonsteroidal anti-inflammatory drugs and opioids, and some patients may benefit from the short-term use of a brace; however, more severe problems will require surgical stabilization.

Pain Associated with Muscle Spasm

This type of pain may be a short-term problem associated with the initial injury or may become a major challenge for management, particularly in patients with a complete spinal cord injury manifested by a classic upper motor neuron lesion with hyperreflexia and clonus. However, muscle spasm pain may also occur in patients with incomplete SCI. The pain is usually delayed in onset and the spasms may be painful or nonpainful. Antispasmodic medications such as baclofen taken by mouth may be effective, however, in severe cases, patients may require the delivery of baclofen via an intrathecal pump.

Secondary Overuse or Pressure Syndromes

Such problems are commonly associated with the abnormal use of structures above the level of spinal cord injury such as the arm and shoulder (11). The pain occurs in innervated regions above the SCI and is thus very common in paraplegics but rare in tetraplegics. The pain is characterized by aching in areas of overuse and is increased by excessive use and also by local pressure. It has been reported that there are degenerative changes present in the shoulders of in 75% of wheelchair users (12). This is not a difficult type of pain to diagnose however it is difficult to protect shoulders from further trauma because of the need for patients to transfer and to maintain mobility. The pain is usually relieved by rest and nonsteroidal anti-inflammatory drugs and sometimes requires the use of opioids.

Visceral Pain

In the 5-yr follow-up study (9) visceral pain was uncommon, being present in only 5% of patients. The characteristics of this type of pain are as follows:

- Delayed onset, burning, cramping constantly present but increased/decreased intensity, abdominal pain.
- Often poorly defined, may be no visceral pathology.
- Visceral pathology must first be excluded/treated – ultrasound/CT scan. ? diagnostic celiac plexus block.

Often no visceral pathology can be found and in this situation the pain is probably best regarded as being below-level SCI pain and treated as such. In our own studies extending over the last 10 yr, celiac plexus blocks have usually been unsuccessful in relieving this type of pain, confirming that it really has no true visceral basis. However, patients with below-level SCI pain will often have the pain markedly exacerbated by visceral triggers such as a bladder infection. This is part of a below-level hyperreflexic response.

Neuropathic Pain

Above-Level Neuropathic Pain

Patients using wheelchairs may be susceptible to peripheral nerve compression (e.g., affecting the upper limb) (13). CRPS Type I and Type II may occur, particularly in patients with cervical injuries (14,15). The mean onset is usually at approximately 24 days, and the incidence has been reported to be approximately 63% in patients with cervical injuries (15). The pain is treated with appropriate measures for neuropathic pain.

Nerve Root Entrapment

This is a variation of at-level SCI pain. The characteristics of this pain are as follows:

- Neuropathic type pain in radicular pattern.
- At-level of SCI and present at injury.

This is an important pain type to diagnose, and it is usually possible to identify abnormalities on magnetic resonance or computed tomographic scan, sensory evoked potentials, and on electromyogram. Not unexpectedly, some patients have such abnormalities, indicating nerve damage, but do not have any pain. As is the case in patients without spinal cord injury, if there is obvious foraminal compression or instability, this will need to be treated surgically.

Segmental Deafferentation Pain

This is also a variant of at-level SCI pain. The characteristics of this type of pain are as follows:

- Pain in 2–4 segments at-level of SCI ("girdle" or "end-zone"pain).
- Unilateral, bilateral (usual) or circumferential.
- Allodynia/hyperalgesia common.
- Early onset first few months. Opioid resistant.

In our experience, patients with this type of pain are often very troubled by the allodynia and hyperalgesia, and this can be very effectively treated by a subcutaneous infusion of lidocaine at a rate of 50–100 mg/h. More recently we have begun to replace the lidocaine infusion with titrated doses of gabapentin. In some patients, spinal cord stimulation has been attempted (where there is residual sensation); however, the results of this have been very mixed. DREZ lesions have

also been attempted with variable results. In severe persisting cases spinal drug therapy may be required.

Cauda Equina Syndrome

This is another variant of at-level SCI pain. This is strictly not a spinal cord injury but a nerve root injury, as the lesion is produced at the very bottom of the spinal cord or somewhat lower.

The characteristics of this type of pain are as follows:

- Nerve root type neuropathic pain.
- Legs, feet, perineum, genitalia, rectum.
- Spinal cord deafferentation leads to "central" pain.
- Nerve root damage leads to spontaneous firing.
- Arachnoiditis.

Because of the potential trauma that may have occurred to spinal nerve roots and meninges, it is not unusual for arachnoiditis to develop and for there to be tethering of spinal nerve roots, producing nerve root damage, neuroma formation, and thus severe mechanical sensitivity that will trigger neuronal firing with slight movement.

Below-Level Neuropathic Pain

This type of pain was present in 34% of patients at 5 yr after SCI (9). Although the incidence of this type of pain is low at 2 wk after SCI, there is a gradual increase over the ensuing years. The characteristics of this type of pain are as follows:

- "Dysesthetic pain," central dysesthesia syndrome.
- Diffuse burning, tingling, aching, throbbing.
- Pain constant, unrelated to position or activity.
- Pain is often increased by infections (e.g., bladder), by sudden noise and by jarring movements.

A double lesion phenomenon has been described in patients with cervical or thoracic cord injuries who develop lower motor neuron signs in the lumbo-sacral segments, in addition to the existing upper motor neuron signs produced at the level of spinal cord injury (16)

Syringomyelia

Syringomyelia is an important diagnosis in patients with SCI because of the potential for development of increased neurologic deficit and the possibility of treatment to reduce such deficit. The initial diagnosis is made on clinical grounds but magnetic resonance imaging scan is required for definitive diagnosis (17,18). The characteristics of this type of pain are as follows:

- Late onset neuropathic pain and increased SCI level.
- Loss of temperature/noxious stimulation response typical but all sensation/motor function may be lost.
- 65% of patients have delayed onset (average 6 yr).
- Constant burning pain ± allodynia.

Quite frequently syringomyelia results from tethering of the spinal cord at the level of spinal injury. Once the cord becomes tethered, the cerebrospinal fluid dynamics are altered, resulting in a gradually enlarging syrinx filled with cerebrospinal fluid in the cord. If feasible, neurosurgical correction with a shunt may be required and in some centers it is held that detethering of the cord is also required.

SCI Pain and Psychological Factors

It is inappropriate to specify a "psychogenic" category of pain in patients with spinal cord injury. On the contrary, psychological factors may contribute to any of the pain types associated with SCI. In patients with SCI, psychological factors can have a major impact on the patient's experience of pain (19). However, it has been reported that pain itself may affect psychological status and is the only complication of SCI that lowers quality of life scores (20). Indeed, pain had more effect on quality of life scores than did the extent of SCI (21).

In summary, there has been a major increase in knowledge of the epidemiology of spinal cord injury pain, the types of pain associated with SCI and the characteristics of such types of pain. An important advance has been the agreement of a special interest group of the IASP on a taxonomy of spinal cord injury pain. A comprehensive chapter on these issues has been provided by Siddall et al. (22) in an IASP text on this subject.

Mechanisms of SCI Pain

Surprisingly, there has been little information regarding mechanisms of spinal cord injury pain until quite recently. Progress has been difficult because of the lack of appropriate animal models. This was further complicated by lack of clarity concerning human SCI pain syndromes and the relationship between any available animal models and clinical pain types in humans. There has been some degree of clarification of these issues and this has been summarized in a recent review (6).

General Mechanisms of SCI Pain

In general there are some broad mechanisms of SCI pain that can be summarized as follows:

- Central pain — spinal/supraspinal neuropathic mechanisms.

- Spinal nerve damage — "peripheral" neuropathic mechanisms.
- Visceral dysfunction — obstipation, urinary tract infections/calculi.
- Soft tissue damage/overuse of skeletal muscles — also spastic syndrome muscle spasm may increase pain.

It is particularly important to note that in many patients with spinal cord injury and pain, so-called peripheral mechanisms frequently interact with central mechanisms. This is particularly seen, for example, in patients with below-level neuropathic pain whose pain may be increased by nociceptive input from an infected bladder or by gut distension associated with obstipation. Even in the presence of a complete lesion, such nociceptive inputs are capable of generating hyperreflexic responses such as an increase in blood pressure or increased muscle tone below the level of the lesion (with reciprocal changes in muscles above the level of lesion), and these effects are able to "jump the lesion" by activating central processes. For example, a sudden increase in blood pressure impinges on the vasomotor center, which is in close juxtaposition with pain control centers in the periaqueductal gray and associated limbic system. Former proposals for afferent input via intact sympathetic afferent fibers have not been confirmed by any substantial data. However, sympathetic nervous system activity plays a part in the above-mentioned neurovascular changes below the level of the lesion.

At-Level SCI Pain

Animal models developed to study this type of pain have characteristics that can be summarized as follows:

- Rostro-caudal spread of central gray matter loss: excitotoxic, neurochemical, inflammatory.
- Increased basal and stimulus evoked c-fos above SCI.
- Increased basal and evoked activity of spinal neurones above and below SCI.
- Increased nitric oxide release in ventral cord and decreased NO in superficial dorsal cord - ? indicating deficit of nitric oxide-rich $GABA_A$ neurones within dorsal cord.

The major underlying deficit in humans with at-level neuropathic pain appears to be a rostro-caudal spread of central gray matter loss that is the result of excitotoxic, neurochemical, and inflammatory processes. In a contusive model of SCI, Siddall et al. (23) reported an increased basal and stimulus evoked activity of c-fos above the level of SCI. Also, there was an increased basal and evoked activity of spinal neurons above and below the level of SCI (24). Studies of nitric oxide release in spinal cord have revealed that there is enhanced release in the ventral cord but a marked decreased release in the superficial dorsal cord. The latter finding may indicate a deficit of GABA neurons, which are known to have a high content of nitric oxide (H. Allbutt, unpublished data). This finding may be of substantial interest because it points to a deficiency of inhibitory influences. It has been proposed that there may be two phases of at-level pain with different mechanisms (6,25). These mechanisms and their implications can be summarized as follows:

- Acutely (1–5 days): decreased $GABA_B$ immunoreactivity – decreased hyperalgesia by $GABA_B$ agonists (e.g., baclofen).
- Chronic phase: ? independent of $GABA_B$.
- Responsive partly to $GABA_A$ (e.g., midazolam intrathecally).
- NMDA – Ca ++ block effective (e.g., gabapentin) – responsive to intrathecal clonidine-morphine.

Some observations of the efficacy of treatment are at least partly supportive of the foregoing mechanisms. NMDA antagonists have been found to prevent hyperalgesia in rat SCI models (26) and in humans with SCI (27). Repeated administration of gabapentin, (putative effect at an NMDA/calcium channel complex) reduces hyperalgesia in rats with SCI (28)

Mechanisms of Below-Level SCI Pain

Early concepts of below-level neuropathic pain derived from clinical literature that focused on a "deafferentation" mechanism resulting from loss of input to central structures connected to the spinothalamic pathway (29). Lesions of the anterolateral cord in monkeys and rats result in over-grooming and/or autotomy below the level of the lesion (30). Also, after anterolateral cordotomy in humans, rodents, and monkeys, allodynia and hyperalgesia may occur (31,32). A study of spinothalamic tractotomy in primates found that there were abnormal patterns of resting and evoked activity in ventrobasal thalamus (33). Recently our group has studied the ventrobasal thalamus in a rat model of spinal cord injury, comparing rats with allodynia versus those with no allodynia. In both allodynic and non-allodynic SCI rats, there was a significantly higher proportion of neurons that fired spontaneously in an oscillatory mode, when compared with neurons in uninjured rats. Of most interest, the evoked responses of neurons in allodynic rats were significantly elevated above those in uninjured rats and neuronal after discharges were more common in allodynic than in non-allodynic rats (34). These findings are of great interest because below-level SCI pain is characterized by being highly labile and is triggered by somatic and visceral input. Once the pain is triggered, it often continues for substantial

periods of time, which is in keeping with the presence of after discharges in the above study.

Relationship of At-Level to Below-Level SCI Pain

Patients who begin with at-level pain often progress to below-level pain (35). However, in some cases both types of pain are present (9). There appear to be some anatomical differences in at-level and below-level SCI pain.

- Cellular (central gray) loss: at-level pain.
- Axonal (peripheral white) loss: below-level pain.

Treatment of SCI Pain: General Treatment Options

If one focused only on the treatment of neuropathic SCI pain, until recently one could say that there was no effective established treatment. However, there are many causes of pain in patients with SCI that are amenable to treatment as indicated under each type of pain discussed above. For example, musculoskeletal pain is very prevalent and can often be ameliorated by practical measures such as re-evaluating the patient's wheelchair in terms of its suitability for their sitting position and transfers. Other musculoskeletal problems in the upper body often need to be addressed because of the increased load that the various muscle groups have been called on to bear. Another important area that has emerged over the past 10 yr is that SCI in the cervical area that is associated with cord tethering may predispose to syrinx formation. The syrinx poses a risk of extension of the spinal cord injury and is unlikely to be completely cured by treating the syrinx alone; it also requires "de-tethering" of the spinal cord. An interesting finding of our longitudinal study is that the majority of patients who report pain in the abdominal region appear not to have any visceral pathology; rather, this pain seems to be a variant of "below-level neuropathic pain." Support for this has been obtained by our performance of celiac plexus blocks in such patients with almost uniform lack of pain relief.

The major problem in patients with SCI is neuropathic at-level and below-level pain. A wide range of pharmacologic approaches has been advocated for treatment but with little evidence of any efficacy (4,36). In 1994 we reported a single patient who responded to the intrathecal administration of morphine and clonidine (37). This finding stimulated a prospective randomized, within-patient, study of morphine, clonidine, and a morphine/clonidine combination. This appeared to be the first controlled study of "spinal combination therapy" via the intrathecal route for any form of chronic non-cancer pain. Of interest, morphine was no more effective that saline placebo; however, in some patients morphine caused an exacerbation of SCI pain. In contrast the combination of morphine and clonidine was clearly efficacious for SCI pain (38). Spasticity is often a problem in SCI patients and may be present alone or in combination with pain. The analgesic properties of baclofen have not been adequately studied in SCI pain. We have reported a single patient who was unable to obtain adequate analgesia with single-agent therapy but achieved control of both pain and spasticity with the combination of intrathecal clonidine and baclofen (39). Discussion of other options for treatment is provided in the IASP monograph published in 2002 (40). A systematic review of combinations of intrathecal drugs that may be options for SCI pain was recently published (41).

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