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Neuropathic pain following spinal cord injury: what we know about mechanisms, assessment and management

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Abstract. – BACKGROUND: In biology, it is easy to understand how a damaged functional system may generate wrong signals, but why this should happen when the system is disconnected is less clear. For this reason, among other pain syndromes, neuropathic pain (NP) following spinal cord injury (SCI) leaves most questions unanswered.

AIMS AND METHODS: Our purpose is to review current knowledge on NP after SCI, focusing on the mechanisms, assessment and management of the syndrome.

RESULTS: The mechanisms responsible for NP following SCI are poorly understood: NP is classically considered a "central pain syndrome" but recent evidence from experimental models reveals a possible "peripheral sensitization". Assessment of NP following SCI is well-established: in addition to clinical evaluation and self-reported scales, many neurophysiological, radiological and microscopic investigations may be performed. The management of NP following SCI is very difficult: evidence of effective drugs is lacking and alternative new treatment approaches yield different outcomes.

CONCLUSIONS: Recently clinical and instrumental tools have increased our knowledge on NP, suggesting that the discovery of new treatment agents will depend on an explanation of what changes after SCI: future research must point in this direction.

Key Words:
Neuropathic pain, Spinal cord injury, Central sensitization, Peripheral sensitization.

Introduction

The nociceptive system works by processing potentially dangerous internal or external stimuli: its physiological response is pain. When pain is caused by non-neural tissues it is called "nociceptive pain", whereas if pain "arises as a direct consequence of a lesion or disease affecting the somatosensory system"[1] with or without adequate stimulation, the term "neuropathic pain" (NP) has been introduced.

Spinal cord injury (SCI) directly affects the somatosensory system and SCI patients experience both nociceptive pain and NP, immediately (> 1 month) after the acute injury or developing later. Many classifications have been proposed to identify SCI patients' pain: the accepted taxonomy is based on the *ad hoc*-formed Task Force of the International Association of the Study of Pain (IASP)[2]. The IASP Task Force divided nociceptive pain into musculoskeletal (bone/joint/muscle trauma or inflammation, muscle spasms, secondary overuse syndrome, mechanical instability), visceral (renal/bowel/sphincter dysfunction, "dysreflexic headache") and NP on the basis of anatomic involvement referred to SCI level: above level (AbL), at level (AtL) or below level (BeL). AbL NP includes compressive mononeuropathies and complex regional pain syndrome, AtL NP includes nerve root/cauda equine compression, post-traumatic syringomyelia and spinal cord trauma/ischemia, BeL NP includes spinal cord trauma/ischemia[3]. Moreover, SCI patients with NP typically complain of sensory phenomena such as allodynia or hyperalgesia in the painful area[4].

From the first cohorts examined, pain following SCI revealed a high (> 60-80%) overall prevalence[5]. Musculoskeletal and AtL pain are the most common and earliest experienced types. BeL and visceral pain occur 2 years after the ini-

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tial injury. NP and visceral pain are more likely to be severe and long-lasting, suggesting that musculoskeletal pain is more treatable by current drugs (non-steroidal anti-inflammatory drugs and opioids).

Thus, NP following SCI is one of the most complex and challenging pain syndromes. This paper briefly describes the current main features of NP, focusing on mechanisms, assessment and management.

Mechanisms of NP Following SCI

The spinal cord close to the site of injury is probably where most anatomic and functional changes occur after injury. Thus, the first studies[6] considered it the "site of origin of the distal burning". However, the recent development of simulating animal models[7,8] has disclosed a broader range of sites responsible for NP following SCI. We first describe what happens in the spinal cord, then in the brain and peripheral structures.

Spinal Cord

Acute ischemic or traumatic damage triggers a series of mutually-related and self-sustained events in the spinal cord[9,10]. Pathogenic insult includes anatomical, neurochemical, excitotoxic and inflammatory alterations. These components lead to a change in spinal neuron function and then to pain.

The cascade does not occur in a programmed sequential fashion but evidence of an influence of sex, strain and gonadal hormones[11] and of selective neuroprotective agents[12] suggests that molecular events are prevalent in the first stage. In particular, inflammation (cytokines, prostaglandins, reactive oxygen species) and neuromodulator (glutamate, GABA, opioid, serotonergic, noradrenergic) agents change expression and function[9,13] producing 3 main effects:

- Activation of microglia[14] and astrocytes from a resting state;
- Different neuronal firing: increased neuron recruitment after stimulation, enhanced irregular background activity, and alterations in sodium currents[15,16] are present and modulated by in situ administration of local anesthetics[6];
- Long-term synaptic plasticity[17], including modified synaptic connection and regulatory proteins, apoptosis or rescuing of neurons, modified regulation of gene transcription/translation[18].

Brain

SCI leads not only to cord atrophy but also to cortical atrophy of the primary motor and sensory cortex[19] and, as occurs in other pain syndromes, e.g. phantom limb syndrome[20], a shift in cortical body representation[21]. Moreover, changes in firing and in thalamic neuron molecules have been found[22]. Thus, functional reorganization of the brain caused by sensory denervation is due to double-speed mechanisms. The first, faster mechanism results from unmasking dormant synapses, while the second, slower but stronger mechanism reflects thickening of the deafferented cortex with growth of lateral, closer regions.

Periphery

Except for mechanical root/nerve insults, NP following SCI is classically considered a "central pain syndrome" and few reports have investigated the morphological and functional evolution of cutaneous structures after SCI[23-25]. Peripheral pain generators may be stimulated in SCI patients with residual spinothalamic tract pathways, mimicking exacerbation of NP[26]. Animal models of AbL NP[27] revealed increased responsiveness of uninjured primary afferent fibers suggesting there is a permanent change in the fibers and /or in the chemical environment in the skin named "peripheral sensitization" [27,28]. Lowering of the threshold to mechanical and heat stimuli in the overlying SCI segments may be considered a human equivalent[29].

Assessment of NP Following SCI

International Consensus recurrently review general recommendations for NP assessment[30,31]. NP after SCI overall adopts the same[32].

The first step is to identify pain as possible NP by definition[1], rejecting any other possible somatic cause. Screening tools, like self-reported scales, in particular DN4[33], are available and useful.

The second step is clinical examination to assess pain intensity, using a visual analogue scale (VAS) or numeric rating scale (NRS): even if it is a subjective estimation of pain, these scales readily provide information on pain evolution over time and the effect of treatment. Clinical evaluation should include an assessment of sleep, mood, and quality of life[34].

The third step is to perform laboratory tests and is mostly confined to research trials. Electroneuromyography is sensitive in assessing any associated damage of the peripheral motor path-

ways[35,36]. Although expensive, laser-evoked potentials (LEP) are useful for assessing the function of the A-delta fiber subcortical pathways and can localize the lesion with precision[37]. MRI is useful to quantify spinal cord damage and its consequences (post-traumatic syringomyelia). Activation brain imaging (PET-fMRI) is an interesting research tool, investigating synaptic changes. Skin biopsy is not much used in SCI patients in contrast with other pain syndromes.

Management of NP Following SCI

Physicians must make every effort to counteract NP because pain affects activities of daily living and rehabilitation[38] and frequently results in depression and suicide[39].

Treatment is rarely successful and a moderate improvement may be achieved only after a combination of more approaches for a long time.

There follows a list of the most effective pharmacological and the most innovative non-pharmacological therapy options, as established in recent review articles[3,40,41]. Nociceptive pain has been excluded.

Amitriptyline (up to 150 mg/die) and pregabalin (up to 600 mg/die) are the only drugs to be justifiably considered for SCI patients. Discrepant results have been reported with lamotrigine and many side-effects with tramadol and other opioids.

Apart from spine stabilization and nerve decompression, good surgical results have also been described with destruction of the dorsal root entry zone[42].

In the area of neuro/psycho-stimulation, transcranial direct current stimulation (tDCS) has led to a transitory reduction in pain with minimal side-effects and good tolerability[43]. Pain was further reduced by combining tDCS with virtual gait self-perception[44,45]. Effective use of visual illusion of walking for NP after sensory system injury (cauda equina) was first applied by Moseley[46] on the basis of NP as a cause of altered cortical body representation and disrupted sensory afferents.

Conclusions

Chronic NP is a common disabling complication of SCI and results in impaired quality of life. Clinical examination and assessment of pain quality and intensity are crucial parts of the diagnostic process. Laboratory evaluations help to elucidate causative mechanisms and much progress has been achieved in recent years. In particular, peripheral sensitization may explain why NP occurs with or without a complete loss of spinothalamic tract function[47] or in other diseases with theoretical pure motor CNS involvement, e.g. locked-in syndrome[48,49]. Further investigations must focus on pathogenesis: discovering targets we may improve our current limited therapeutic weapons.

Statement of Interests

Authors disclose no personal or funding interests about this paper drafting.

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