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mention Neuropathic pain: We need more interdisciplinary and holistic treatment

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1. Introduction

In most cases pain is a result of irritation of primary nociceptive afferents by traumatic stimuli and processing of this activity within the nociceptive system. In some cases, however, pain may be generated by the nervous system itself, without adequate stimulation of peripheral nociceptive endings. This type of pain is called “neuropathic”. The International Association for the Study of Pain (IASP) recently updated the definition of neuropathic pain, saying that it is “pain caused by a lesion or disease of the somatosensory system” (Treede et al., 2008). This definition clearly shows that the lesion in the nervous system must be within the somatosensory system. Neuropathic pain is not a single disease but a syndrome caused by a range of different diseases and lesions which manifests clinically as complex of symptoms and signs. The underlying mechanisms of these different conditions are multiple. Some of these mechanism are known, but some are not. Prior to confident diagnosis of neuropathic pain, other types of pain should be excluded. Neuropathic pain needs to be distinguished from pain due to secondary neuroplastic changes in the nociceptive system resulting from sufficiently strong nociceptive stimulation, e.g., inflammatory pain. It also needs to be distinguished from musculoskeletal and other types of pain that arise indirectly in the course of neurologic disorders (Treede et al., 2008).

Neuropathic pain is related to central or peripheral nerve injury, due to nerve compression, ischemia or laceration. Clinical symptoms and different treatment strategies are well known among neurologists, anaesthesiologists, neurosurgeons, orthopaedic and hand surgeons and physio- and occupational therapists (Bahm, 2017; Baron, 2004; Zyluk, 2004, 2014).

The natural history includes a frequent evolution into *chronic* pain, characterized less by the time duration, than by the inability of the body to restore its physiological functions to normal homeostatic levels (Loeser & Melzack, 1999). Chronic or persistent pain is actually defined as being continuous or recurrent and of sufficient duration [at minimum 3–6 months] and intensity to adversely affect the patient́s well being, level of function and quality of life (ACPC Resource Guide, 2012).

The specific pathophysiology of neuropathic pain is related to its underlying central or peripheral nerve pathology: trauma, scar, tumour, inflammation lead to a loss of the physiological function and regulation of the interaction between a nociceptive stimulus and the physiologic response. The normal pathway turns into a vicious circle; where even non nociceptive stimuli may cause pain (like allodynia) or pain becomes « automatic ».

Additional symptoms occur, like *catastrophizing* (de Boer, Steinhagen, Versteegen, Struys, & Sanderman, 2014), i.e. the negative expectation and inappropriate handling of the emotional context before and after the pain event.

Affecting the upper limb, neuropathic pain might be the major issue in cervical root damage (including traumatic root avulsion or stenosing cervical spine pathology), brachial plexus and peripheral nerve injuries, syndromes like the complex regional pain syndrome [CRPS] and mainly its type II [formerly named “causalgia”] and finally ischemia. In severest brachial plexus injuries in the young adult (motorcycle

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accidents) which include multiple nerve root avulsions (reflecting a severe spinal cord trauma), responsible for severe neuropathic deafferentiation pain, associated with other types of pain, this pain problem ranges at the top level of any consultation, even before demands about functional reconstruction. It is important to note that neuropathic and other types of pains are often present in the same patient (e.g., degenerative spine disease). Even in cases of definite neuropathic pain, a coexisting inflammatory pain may be clinically more important.

The actual treatment strategy is multidisciplinary, including medication (neuroleptic, antidepressive and anticonvulsive drugs), surgery (decompression, nerve repair, neuroma surgery, implantation of stimulation devices) and rehabilitation (sensory re-education, mirror therapy, motor relearning). Nevertheless, the current therapy of neuropathic pain is frequently ineffective, resulting in insufficient pain relief in many patients. This relatively poor response to the treatment is likely related to mistargeting relevant pain-generating mechanisms in individual patients.

Even when undergoing physio- and occupational therapy, the patient frequently becomes a chronic therapy consumer, passive, accepting the positive and negative treatment effects and getting dependant on external factors. Only in new approaches including neuroplasticity (graded motor imagery (Moseley & Flor, 2012), mirror therapy), an attempt is actually made to return actor ship to the patient himself and to regain autonomy.

With this review article, the three authors bring together different lessons learned from long-standing clinical experience, together with an individual holistic medical attitude, towards those patients who run out of classic medical pathways because of pain exacerbation or recurrence, ineffective prior treatment, severe drug side effects, and a general deterioration of quality of live, work and leisure capacity, ending in lost social integration.

2. The challenge

Every patient experiencing neuropathic pain has his individual and specific medical and personal history, making him so different from all others. He describes the pain in his words, which are sometimes difficult to be listened (Hearn, Finlay, & Fine, 2016). He has his individual response to prior treatment modalities, more or less effective in the acute or chronic phase. Obviously, all these patients are so challenging for the health care provider due to the need of patience, understanding, empathy, creative searching of new solutions (like a hidden and untreated organic pathology-read del Pinal, 2013), handling of pitfalls, analysing the individual life impact, ranging from compensation to severe depression. In our medical world evolving into more subspecialisation, rare are the colleagues who are willing to re-invest an holistic, integrative approach; more time and energy consuming, especially in the field of chronic neuropathic pain.

Evidence based medicine actually provides puzzle pieces (e.g. Song, Lu, Chen, Geng, & Wang, 2014) of value in a more global approach to treat, and rapid changes in neuroscience (neuroplasticity) will force us to remain concordant with newer achievements in basic and clinical science.

3. Pathophysiology

As pain is an outmost *subjective* experience, each patient should be able and encouraged to describe it in his proper words; and only after than an objective assessment attempt e.g. of pain intensity by the VAS (visual analogue scale) should be made. The Short Form McGill Pain Questionnaire is a self-report questionnaire which provides a comprehensive assessment of subjects' pain. It includes a 0–10 visual analogue rating scale of pain intensity as well as a comprehensive list of pain descriptors that capture the quality of that pain. It has been shown to have good validity and reliability (Graham, Bond, & Gerkovich, 1980). This instrument may be useful in more precise characterising patients' self-reported experience of pain.

The surrounding of pain attacks comprises the before and after: *Before*, there might be pain anticipation due to previous negative experience, and a negative expectation, affecting self-confidence. This characteristic is related to a specific brain area (the so called MCC midcingular cortex).

The *pain perception itself* is based on a specific nerve conduction system: peripheral nociceptors located in the skin, deep tissue or viscera are activated by either intense mechanical or various noxious (e.g. heat, chemicals like bradykinin) stimuli. The response is transferred to the lateral part of the posterior medullar horn (»Lissaueŕs tract »), respectively either by rapid *A delta* fibres (»first pain », well tolerated, inducing the withdraw reflex) or unmyelinated slow *C* fibres (»secondary pain », badly tolerated). A third « deep » pain type comes from muscles and viscera.

In the posterior horn, the various inputs converge on a second neuron, therefore called « *wide dynamic range (wdr)* », with a strong modulation through *Aß* sensible afferent nerves (glutamate-dependant), descendant inhibitory tracts (serotonin-dependant) or an inhibitory interneuron (delivering endorphins).

In 1965, Melzack and Wall Melzack and Wall (1965) described the « *gate control* » theory which describes how peripheral and descendant tracts may inhibit nociception at the medullar level- examples of an endogenous pain- control system originating both from the brain (explaining how hypnosis, acupuncture, meditation and placebo could act on nociception) and from peripheral stimulation (topographic skin pressure reduces deep pain).

Moreover, CNS pain processing (concerning location and intensity) is strongly influenced by an affective, behavioural component acting on the perception and interpretation of pain (the « unpleasantness » of the pain perception) which is open to various training modalities.

After the painful experience, a more or less huge emotional response follows, summarizing the unpleasant experience.

In chronic neuropathic pain (Boogaard et al., 2015) and complex regional pain syndromes (CRPS type I and II extensively described by Harden et al., 2010, 2013), specific pain phenomena may arise:

Where primary *hyperalgesia* is characterized by a double effect, first on the injury site by lowering the threshold for mechanical and thermal stimuli, and secondarily on the healthy tissue around, the so called « secondary » hyperalgesia follows a first nociceptive stimulus and is associated with a lowered threshold for subsequent mechanical stimuli-the later being found in neuropathic conditions.

In *allodynia*, a non noxious stimulus leads to a painful response/experience.

4. Actual treatment summary

The direct central neurosurgical approach is the thermocoagulation of the DREZ (dorsal root entry zone) described by Sindou (1972–2005) (Mertens & Sindou, 2000); main risks are collateral damage and recurrence.

Peripheral re-targeting may be tried by nerve transfers: e.g. the transfer of sensible intercostal nerves onto the lateral part of the median nerve (Socolovsky 2016) or the use of the contralateral C7 root.

Stimulation devices like transcutaneous electrical nerve stimulation (TENS) might be applied temporarily (and remain external) or become permanent (and than are implanted).

Spinal cord stimulation therapy is based on the assumption that electrical stimulation of the spinal cord (SCS) engenders spinal cord-mediated analgesia and anti-inflammatory effects (Taylor, Van Buyten, & Buchser, 2006). There is moderate evidence for the effectiveness of the spinal cord stimulation in giving some reduction in pain symptoms in CRPS patients.

Neuromodulation procedures not only include SCS but also Peripheral-Nerve-Stimulation (PNS) and Dorsal-Root-Ganglion (DRG)-Stimulation. Several medical societies and national/international