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Posttraumatic peripheral neuropathic pain and CRPS in the upper limb

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Abstract. The term of ”complex regional pain syndromes” (CRPS) was introduced by IASP (*International Association for the Study of Pain*) in 1994 and represents a group of algic disorders that may develop as a disproportional consequence of a minor trauma (contusion, fracture, postsurgical), usually in one extremity. There have been described 2 types of CRPS I, previously known as sympathetic dystrophy, develops following trauma with minor lesions and without obvious neurological impairment (with fractures, sprains, contusions or cutaneous lesions). CRPS II or causalgia has similar signs and symptoms and develops after trauma with important peripheral nerve injuries (10-12).
Neuropathic pain therapy is often inefficient regarding nociceptive pain. Knowledge of the patient's medical history related to neuropathic pain and using validated assessment tools are essential for differentiating neuropathic pain from nociceptive pain and to estimate the importance of the neuropathic component of pain from various pain syndromes.
In 2007, International Society for The Study of Pain (IASP) proposed the following definition for neuropathic pain as ‘‘pain caused by a lesion or disease of the somatosensory system’’ (13). ”Diseases” are pathological processes such as inflammatory, autoimmune or dysfunction of ion channels. ”Lesions” are minor detectable lesions. Diseases and lesions of nervous system elements others than somatosensory component determine nociceptive pain. Spasticity and muscle pain related to motor system diseases and lesions are not being associated with neuropathic pain.
Keywords: *nerve injuries, algic disorders, sympathetic dystrophy*.

Neuropathic pain definition

Modern research on neuropathic pain showed that traumatic peripheral nerve injuries determine important changes of the sensory component of the nervous system. Those changes differentiate neuropathic pain from other chronic pain types, such as chronic nociceptive pain from osteoarthrosis, in which case the nociception is not impaired (1).
Posttraumatic peripheral neuropathic pain results from mechanical trauma to the peripheral nerve most frequently related to car accidents, work accidents or in domestic context (2, 3). According to WHO, 3.200.000 experience posttraumatic disabilities after car accidents (4).
Besides classical neuropathic syndromes such as phantom limb pain, there are posttraumatic algic states with common clinical features. These syndromes previously known as reflex sympathetic dystrophy, Sudeck dystrophy, causalgia, shoulder-hand syndrome or algodystrophy are in present grouped under the umbrella term of ”complex regional pain syndromes” (CRPS) (1). The term CRPS was introduced by IASP (*International Association for the Study of Pain*) in 1994 and represents a group of algic disorders that may develop as a disproportional consequence of a minor trauma (contusion, fracture, postsurgical), usually in one extremity (5-9).
There have been described 2 types of CRPS I, previously known as sympathetic dystrophy, develops following trauma with minor lesions and without obvious neurological impairment (with fractures, sprains, contusions or cutaneous lesions). CRPS II or causalgia has similar signs and symptoms and develops after trauma with important peripheral nerve injuries (10-12).
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Diseases and lesions of nervous system elements others than somatic-sensory component determine nociceptive pain. Spasticity and muscle pain related to motor system diseases and lesions are not being associated with neuropathic pain.
Also, is important to establish the peripheral or central origin of pain, taking into account the topography, clinical signs and pathophysiological mechanisms being different.

Classification
In clinical practice, neuropathic pain is classified according to the etiology and anatomical topography of the injury (12). There are 4 major types of nervous system impairment: peripheral painful neuropathies (for example, traumatic, ischemic, inflammatory, toxic, metabolic or hereditary), central type pain syndromes (for example, in stroke, multiple sclerosis, spinal injury), neuropathic complex pain disorders (CRPS) and mixed pain syndromes (nociceptive and neuropathic pain). In many chronic pain syndromes there are involved both nociceptive and neuropathic processes. Those mechanisms can explain the various symptomatology (mixed pain syndromes) (1). The outcome can vary from relatively mild to chronic pathology, with a major impact on daily functioning and quality of life.

Clinical signs in complex regional pain syndromes
CRPS develops usually in the extremities, following fractures, surgery, prolonged immobilization, peripheral nerve injury, etc. It usually manifest in the distal part of the extremity, but pain may radiate proximally or to other body parts. Upper extremities are most frequently impaired. Pain is continuous, spontaneous, regional, like burning, and does not respect the anatomical distribution of a peripheral nerve (11). Symptoms can install gradually after the trauma (14-17). Immediately after the trauma, CRPS is difficult to detect because of the similar posttraumatic symptoms (18).
There was estimated that 50% of the patients with CRPS develop a chronic pain syndrome and disability (12). Pain is disproportional to the trauma severity and associates signs of neurogenic inflammation, osteoporosis and other signs such as (19-22): sensory disorders/dysfunction (burning pain, mechanical hyperalgesia, hyperesthesia, allodynia, sudomotor disorders (oedema and excessive perspiration) and vasomotor disorders (skin temperature and color changes); trophic changes of skin, hair and nails; motor function impairment: voluntary movement impairment, reduced range of motion, hypotonia, tremor, joint stiffness, coordination disorders, dystonia and muscle spasms.
Pain related to peripheral nerve injury has specific clinical features (23). If the injured nerve is a mixed peripheral nerve with a cutaneous branch there is an area of abnormal sensation. The maximum pain experienced by the patient corresponds to an area of sensory deficit, specific for neuropathic pain. Sensory deficit is usually related to nociceptive or thermal stimuli (1).
Paresthesia determine discomfort, but are not painful. Positive signs are sensations of permanent and intermittent spontaneous pain (are not induced by stimuli). Many patients with neuropathic pain reported also stimuli induced pain and hypersensitivity. Patients report frequently mechanical hypersensitivity and consequently, hypersensibility (1). There are two types of hypersensibility: allodynia - pain as a response to non-nociceptive stimuli, and hyperalgesia - painful hypersensitivity to nociceptive stimuli.
A small number of patients with peripheral nerve injury have a hypersensitive syndrome, without evident signs of sensory deficit. Usually, neuropathic pain is intermittent, like burning, with unusual paresthesia. Although these characteristics are not universally present in all neuropathic pain states, when they are, the diagnosis of neuropathic pain is probable (1).

Peripheral sensitization of primary afferents
Peripheral sensitization of primary afferent neurons has been described in patients with painful peripheral nerve injury. An example is decreased thermal algic perception. Cutaneous cold hypersensibility (hyperalgesia) is frequently in patients with posttraumatic neuralgia and in chronic complex regional pain syndromes (1).
Neuropathic pain persists more than nociceptive pain, is provoked by stimuli that are normally not painful and is influenced only by specific medication (14).

Neuropathic pain is severe, impairing patient's life quality, being associated with anxiety and depression, sleep disorders and disability (24, 14). It may develop after trauma with peripheral nerve injuries or after surgery (25, 3, 14). Even in patients with minor changes in neurologic tests, in peripheral nerve injuries neuropathic pain is spontaneous and determine areas of hypoaesthesia and/or hyperaesthesia (14).
Ciaramitaro et al. have published in 2010 an epidemiological study regarding traumatic peripheral nerve lesions and neuropathic pain. In the first year they analyzed 211 cases, most of them young males, the lesions being predominantly in the upper limb. 50% of them presented neuropathic pain, mild to severe in 79% of the patients. Most frequently pain was located in radial and ulnar nerve areas. The presence of neuropathic pain has been correlated with decreased quality of life in patients with posttraumatic neuropathies (3, 14).
Taylor et al. (2010) compared two groups of patients with postsurgical peripheral nerve lesions (median and cubital). Patients with neuropathic pain had severe sensory-motor deficit and impaired nerve recovery (26, 14).

Incidence and etiology of CRPS

The incidence of CRPS was analyzed in retrospective and prospective studies. They have been reported most frequently after distal radius fractures (27-29, 21, 19). Sandroni et al. reported an incidence rate of CRPS of 5.46/100.000 person years in the general population (Olmsted County, USA) (30, 8).
CRPS impairs 3 times more women than men and may develop in any age, with a higher incidence between ages of 50 and 70 years. Over 50% are posttraumatic. In 44% of cases, the trigger was a fracture (8). Most of the studies were prospective. The incidence was 1-2% in retrospective studies regarding distal radius fractures and up to 38% in prospective studies (31), probably due to a lack of uniform and specific diagnostic criteria (11). Other reported causes are sprains (18%) and surgery (12%) (8). Also, prolonged immobilization, peripheral nerve injury and compressive syndromes may determine CRPS (28).
Clinical signs, especially those of autonomic dysfunction and Leriche findings on pain relief through sympathyectomy sustain the role of the nervous sympathetic system in CRPS etiology (32, 9).
Pain from complex regional pain syndromes has a component of neuropathic pain (33, 9), being generated and maintained by peripheral nerve sensory fibers and also is inflammatory, nociceptive and functional (9). Quantitative sensory testing suggests the role of inflammation in acute CRPS. Nociceptive pain may be caused by tissue lesions, as a result of the initial trauma or by secondary tissue lesions determined by edema and trophic changes, hypoxia and acidosis (34-35, 9).

CRPS pathophysiology

It has been suggested that trauma and rare diseases may determine disorders of the central nervous system. CRPS may be a disorder of sensory, autonomic and motor functions (11). Besides peripheral factors, CRPS may be also determined by neurogenic inflammation, immune factors and genetic predisposition (36-39, 11).
Spatial distribution of pain, allodynia to mechanical and thermal stimuli and hyperalgesia suggests the role of both peripheral nervous system and central nervous system in the pathophysiology of complex regional pain syndromes (40, 41, 20, 9).
Some symptoms suggests that neurological dysfunction is not limited to the peripheral and autonomic nervous system, but there is also a distortion of body image and cortical function reorganization (42, 22), at the cortical level.
In the study of Pleger et al., cortical representation of painful hand was significantly reduced compared to contralateral normal hand (43, 11). Maihofner et al. reported that cortical representation of the normal contralateral hand was significantly more reduced than in the CRPS impaired hand, considering that is due to the reorganization of the primary somatosensory cortex (44, 11). It has been found that cortical reorganization is CRPS nonspecific, being reported also in other algic states (11) and it becomes normal along with the recovery (45, 11).

Therapeutical management of CRPS

The mainly therapeutic goals in CRPS are pain control and functional restoration. Findings of different studies showed that early diagnosis of CRPS and prompt initiation of individualized therapy are essential to improve patient outcomes. Because of the complex symptomatology, in the therapeutically management of CRPS there may be involved different specialists - in anesthesiology, surgery, neurology, rheumatology, physical medicine and rehabilitation (8).

Besides analgesic and antiinflammatory pharmacological therapy there may also be useful physical therapy, occupational therapy and psychotherapy (11). Active physiotherapy is essential for functional restoration (46, 11). Immobilization and splinting are the first physical modalities recommended. Also elevation of the distal part of the extremity, therapeutic massage and isometric exercises are gradually introduced into the therapeutic programme considering therapy must not exacerbate the pain (47). Hydrotherapy (alternating heat and cold baths), transcutaneous electrical nerve stimulation (TENS), and a stress loading program of traction and compression exercises have also been shown to be effective in CRPS (48, 47).
Functional neuroimaging studies reported the increase of motor cortical representation of the affected extremity (43) and reduced cortical representation of primary sensory cortex (44). It has been considered that the reorganization is reversible and that it is correlated with pain. Also, pain relief was correlated with a normalization of primary cortical sensory area (45).
Two interventions were developed based on the concept of sensory-motor information manipulation in the impaired extremity: mirror therapy (first introduced for phantom limb pain therapy) and prism adaptation (49- 53, 11, 22). Mirror therapy may help for magnifying range of motion and pain relief in patients with CRPS (50). Patients execute synchronal bimanual movements while they are looking the reflection of nonimpaired extremity in a mirror placed in the sagittal midline, having the illusion of a normal functional hand (50, 22).
It has been observed that pain is triggered by seeing an object approaching the impaired extremity (54, 22, 41) and may be increased when the patient looks at the object through magnifying lenses. Also it decrease when watching through lenses that reduce the images (55, 22). These findings suggested the pathological cortical reorganization and the existence of an extension of neural representation of peripersonal space (22).

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