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Review
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CENTRAL PAIN: MECHANISMS, SEMIOLOGY AND TREATMENT

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Summary

Pain problems associated with lesion, disorder or dysfunction of the central nervous system are a common and prominent problem. The objective of this review is to summarize recent advances in our understanding of the etiology, clinical presentation, and treatment of central pain (CP), with emphasis being placed on studies published within the recent years. The incidence, qualities of the pain experience, associated sensory abnormalities, and other characteristics are discussed. Particular attention is paid to CP associated with stroke as the most prominent and best studied of the many CP problems. In general, there is poor understanding of the pathophysiology of CP, problems are often severe and intractable, and treatment is typically difficult. The goal of treatment should be pain reduction rather than complete pain relief. Recent studies have indicated possible roles for tricyclic antidepressants, antiseizure medications, and motor cortex stimulation in the treatment of CP. Surgical procedures have been used for specific causes of CP, but no one surgical technique helps relieve pain over the long term in all CP patients. Perhaps because of the lack of clinical trials, treatment is still largely based on traditional prescribing methods and anecdotal evidence. Our poor understanding of the etiology of central pain and the relative lack of effective treatments emphasize the need for further research into this disorder.

Key words: central pain; etiology; treatement.

1. INTRODUCTION

First described in 1883, central nervous system (CNS) lesions are frequently overlooked as a cause of pain, predominantly because of a lack of knowledge about its characteristics [1]. However, so-called central pain (CP) states are far

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from uncommon. They affect approximately 8% of stroke patients, 10% of individuals with Parkinson's disease, 25% of multiple sclerosis sufferers, over 50% of individuals with spinal cord injuries (SCIs), and up to 80% of patients with syringomyelia [2-6]. In addition, CP has been described under more unusual circumstances such as with vascular malformations, epilepsy, and after neurosurgery and subarachnoid hemorrhage. Less is known about the prevalence and characteristics of CP in other CNS diseases, and the lack of clear diagnostic criteria for CP makes the diagnosis difficult. However, in spite of its prevalence, CP remains one of the most challenging syndromes for physicians to treat. Although there are still many aspects of CP that remain poorly understood, recent developments in the past few years have shed new light on its pathogenesis and treatment.

2. CENTRAL PAIN CONDITIONS

Central pain is defined as *„pain initiated or caused by a primary lesion or dysfunction of the CNS"* by the International Association for the Study of Pain (IASP) [7]. Recently, a more concise definition has been introduced suggesting that central pain is *„pain arising as a direct*

consequence of a lesion or disease affecting the central somatosensory system".[8] Following this new proposal, the prerequisites for the diagnosis of definite central neuropathic pain are:

- the pain in a neuroanatomically plausible pain distribution;
- a history of a relevant lesion or disease affecting the central somatosensory system;
- negative or positive sensory signs confined to the somatotopic representation of the body within the CNS;
- a diagnostic test confirming a lesion or disease explaining the presence of neuropathic pain [8].

The prevalence of shoulder pain in stroke patients has ranged between 11% and 14% and for central post-stroke pain (CPSP) between 8% and 35% [9]. The difference in the prevalence of CPSP is due to variations in inclusion criteria, the definition of CPSP and timing of the study.

In Parkinson's disease, chronic pain may arise because of musculoskeletal disorders, radiculo-neuritic syndromes, or dystonia [10]. In addition to these types of pain, pain may be present with no obvious underlying mechanism and is thought to be a direct consequence of the disease, namely a central pain. This

type of CP is characterized by painful sensations described as stabbing, aching, and burning, predominantly in the more affected side and 'off' condition [10,11]. In patients with brain trauma, lesions of the somatosensory pathways are often obvious and the diagnosis of CP may thus be more straightforward. A systematic study of patients with brain trauma showed that chronic pain in traumatic brain injury resembles that of other CP patients [12].

3. MECHANISMS OF CENTRAL PAIN

In a classic report published in 1906, Dejerine and Roussy described six patients with intolerable and persistent pain, accompanied by sensory and motor deficits as a result of lesions of the thalamus [13]. Since then, CP has been described after other insults to the CNS – namely, as CPSP. After detailed studies of selective neurosurgical interventions, Cassinari and Pagni suggested that interruption of the spinothalamocortical pathways is the single common abnormality found in individuals with CP [14]. The involvement of these pathways may explain how lesions in the spinal cord and brain outside of the thalamus can also generate CP. In fact, disorders of the spinal cord such as traumatic injuries and syringomyelia are probably associated with the highest incidence of CP [3,4,15]. This may be caused by the large relative size of the pain pathways in the spinal cord compared with those in the brain. Over the years, many theories have been put forward to explain the phenomenon of central pain. First expounded on by Head and Holmes in 1911, the idea that the release of the normal inhibitory function by lesions in the CNS may be responsible for central pain gained renewed prominence in the work of Craig and colleagues [16-18]. According to Craig and Bushnell, the sensations of pain and temperature are integrated, with innocuous cold normally inhibiting central pain processing [18]. Disruption of this thermosensory integration results in the loss of coldinhibition of burning pain. An earlier theory holds that it is the reticular thalamic nucleus that is responsible for suppressing the sensations of central pain and hypersensitivity [19,20].

Since Riddoch described the clinical features of patients with CP in 1938, dysfunction of the sympathetic nervous system has been implicated in the disorder [21]. In 1968, Garcin described autonomic disturbances in some patients with CP as manifested by „modificiations in temperature" [22]. In a study performed by Bowsher, a majority of patients with CP exhibited impaired thermal perception and changes in skin temperature on the affected side, indicating possible autonomic dysfunction [23]. In that paper, other signs of autonomic instability in patients included `falling asleep easily' and pain aggravated by orgasm. Other

authors reported that a majority of CP patients suffered from cold allodynia and exacerbation by cold weather [24,25]. Lending further credence to the implication of sympathetic mechanisms are reports of pain caused by CNS lesions being alleviated by sympathetic nerve blocks [26].

Through experimental models of central pain, we have gained more knowledge of CP mechanisms. Gain in neuronal excitability, loss of inhibition, and increased facilitation are thought to contribute to a central sensitization and disinhibition of pain pathways [27,28]. Recently, there has been an increased focus on the interaction between inflammation and neuropathic pain. Activated microglia was found to maintain neuronal hyperexcitability in the spinal cord through an extracellular signal-regulated kinase (ERK)-regulated prostaglandin E2 signaling mechanism [29]. Furthermore, a spinal cord injury was found to trigger remote changes with upregulation of the microglia activator cysteine–cysteine chemokine ligand 21 (CCL21) and induction of microglia activation in the thalamus, changes that were associated with pain behavior [30]. Another study also found the chemokine CCL 2 (monocyte-chemoattractant protein-1) to be a possible candidate of integrating inflammation and central neuropathic pain after SCI [31]. In addition to animal studies pointing towards a role of brain mechanisms in pain following spinal lesions, human brain imaging studies emphasize supraspinal pain mechanisms.

4. PATOPHYSIOLOGY OF CENTRAL PAIN

Many years after an already mentioned Head and Holmes proposed theirs disinhibition theory – according to which injury to the lateral thalamus sets the medial thalamus free from its control – it was found that the lesions anywhere in the spinothalamocortical pathway lead to prominent over-activity of the lateral thalamus [16]. In either situation, CP is associated with impaired sensation evoked by cotton whisp, vibration, roughness, heat and cold. The essential component of this hypothesis is that discriminative sensory deficit in CP results in disinhibition, which gives rise to spontaneous pain or allodynia. Hyperalgesia or allodynia are probably an integral component of CP. In earlier studies, partial sensory loss of spinothalamic modalities was considered necessary for the development of CP [13,32]. This, however, is not sufficient, as spinothalamic deficit, manifested by loss of thermal sensation but without pain, is found in more than half of patients [2]. It is therefore not possible to predict the development of CP by documenting sensory loss. The most likely mechanism for hyperalgesia and partial sensory loss in a body part with normal somatosensory function in a

nonpainful body territory is central sensitization of the third order neurons that have been partially deafferented [33]. In the clinical setting, central sensitization can be assessed by mapping the hypersensitive areas, psychophysiological measurement of different thresholds, and response to various stimuli [33]. The specific neuronal populations which are sensitized in CP are not well known, but certain thalamic nuclei are likely to be responsible.

Reticular nucleus surrounding the dorsal and lateral aspect of thalamus produces GABA-ergic inhibition of relay cells. Groups of deafferented cells in the reticular formation are capable of generating intrinsic bursting activity, which results in a vicious cycle. The corticothalamic axons traverse through the reticular nucleus and innervate these cells by collaterals; hence, cortical lesions may also influence the firing pattern of reticular neurons. In neuropathic pain, spontaneous neuronal activity is found in the mediodorsal, centrolateral, centromedian, and parafascicular nuclei as well as principal sensory nuclei (ventralis caudalis). The shift of thalamic neuronal activity from rhythmic burst firing to single-spike activity is determined by serotonergic, noradrenergic, and cholinergic input of thalamic neurons. Noradrenaline originating from the locus ceruleus and serotonergic pathway from dorsal raphe nuclei mediate thalamic burst firing by acting through reticular and relay nuclei [34]. The beneficial effect of amitriptyline and duloxetine may be mediated through the above-mentioned mechanisms. Excitatory aminoacids, such as N-methyl-d-aspartate, may mediate nociceptive or nonnociceptive inputs to the thalamic nuclei [35]. C-diprenorphine PET studies in CP have been used to evaluate the distribution of opioid receptors; these studies have demonstrated a significant decrease in opioid receptor binding, not only in thalamus contralateral to pain, but also in insula, anterior cingulate and secondary sensory cortex. The decrease in opioid receptor binding may be due to an increase in endogenous release, internalization or dysregulation of receptors and loss of neurons carrying these receptors [36].

5. CLINICAL FINDINGS

It is not uncommon for patients to borrow terms from the taxonomy of nociception, or they may invent bizarre, vague terms to describe what they are feeling. Consequently, patients may describe dysesthetic types of sensations, i.e., painful sensations that may be poorly localized and may vary dramatically from one day to the next.

CP patients often experience superficial and deep pain, sometimes separately, but in most cases concurrently. Pain is constant in 85% of patients, is inter-

mittent but daily in 15%, and occurs on alternating sides in 7%. The burning component is the aspect of pain patients complain about most frequently, but aching, pricking, and lancinating are also qualities common to CP with a supraspinal source.

Clinical findings include qualitative, spatial, and temporal findings. Qualitatively, these patients can have allodynia, dysesthesia and paresthesias. Spatial manifestations include abnormal radiation of pain, poor localization, and impaired discrimination. Temporally patients can experience a complex spectrum of sensation and can exhibit abnormal latencies from the point of stimulation, with after-sensation and sumation. Adaptation and habituation can also occur [37].

Clinical examination and testing of CP patients should include interviewing the patient regarding symptoms of dysesthesias, hyperesthesias, and paresthesias as with burn ins pain experienced constantly or induced by light touch. Warm and cold allodynia symptoms volunteered by the patient should be verified with specific testing. If available, quantitative thermal sensory testing should be used to determine sidc-to-side asymmetries in thresholds to coding, warmth and heat pain; this is the most sensitive technique. Testing for cold may be done at the bedside using a flat metal handle wiped with alcohol, air dried, and applied to the skin. Also, ethyl chloride spray or an ice cube may be used and provides a more intense stimulus. Since most, if not all, CP patients haye some disturbance of sensation, especially temperature alterations-testing and interviewing the patient regarding this is crucial to the diagnosis of CP [38].

Central pain after a stroke (CPSP) has varied and often bizarre characteristics. Disruption of normal sensory pathways may lead to abnormal processing of normal sensory stimuli. This dysfunctional activity within the CNS has certain diagnostic patterns, such as burning pain worsened by touch. Characteristic symptoms of central pain can be identified by the acronym "**MD HAS CP**":

- **M**uscle pains, described as cramping, band-like constriction, as well as crushing, may be quite distressing and disabling for post-stroke patients.
- **D**ysesthesias are the most common abnormal sensations experienced by individuals with CPSP. The characteristic abnormal, unpleasant, and poorly localized sensations are extremely distressing to the patient because they convey no useful sensory discriminative information. Centrally evoked dysesthesias are characterized by delayed onset after stimulus (temporal or slow summation), most often resulting in a burning sensation.
- **H**yperpathia, due to CNS disinhibition, involves a heightened response to noxious stimuli (evoked pain). Injury within the spinothalamic tract is believed to give rise to these pathologic sensory phenomena.

- **A**llodynia is a classic hallmark that is present in more than 50% of patients with post-stroke pain. It involves interpretation of nonpainful stimuli (e.g., thermal, touch) as being painful or the sensation of pain in a location other than the area stimulated.
- **S**hooting/lancinating pain is intermittent pain with clear sensory discriminative characteristics. A patient with this presentation has little difficulty in identifying the location of the pain, unlike the patient with dysesthesias.
- **C**irculatory pain is described as pins and needles, stings, jabs, or walking on broken glass. This pain may be mistaken for peripheral neuropathy or for a result of poor circulation.
- **P**eristaltic/visceral pain may be expressed as bloating, or fullness of the bladder, as well as burning pain with urinary urgency [39].

6. TREATMENT

6.1. Pharmacological treatment

CP is a difficult condition to treat, and pain reduction rather than pain relief has to be the goal of the treatment. Conventional analgesics and opioids have been noted to be ineffective [40,41]. According to the results of an uncontrolled study, only 20% of patients with CP reported a brief reduction of pain after IV morphine, and there are no trials indicating a good efficacy of oral opioids in CPSP [42].

Numerous other drugs have been used in the treatment of CP. Despite the high frequency of this disorder, its severity, and its great impact on quality of life, there is amazingly little scientific evidence on how to treat CP. Randomized controlled studies are rare and include only small numbers of patients. Some of the studies include patients with peripheral neuropathic pain – which is sustained by specific peripheral mechanisms and thus might respond differently to pharmacologic intervention [43,44].

Amitriptyline was the first oral drug proven to be effective in CPSP in a small placebo-controlled, crossover study [25]. Recently, lamotrigine was shown to be a well tolerated and moderately effective compound for the treatment of CPSP in the largest placebo-controlled study conducted to date [45]. As a consequence, amitriptyline and lamotrigine should be regarded as drugs of first choice.

Mexiletine and phenytoin have demonstrated efficacy in a small number of patients in open studies [46,47]. Carbamazepine, often used in the treatment of CP, failed to show effectiveness in a placebo-controlled study, and its use as add-on therapy in CP is supported by some experts opinion only [25,37]. The novel anticonvulsant gabapentin has shown promising effects in a few patients

with CP [48,49]. Its mechanism of action has not yet been fully elucidated, but it appears that there is an effect beyond the membrane-stabilizing properties. Its good safety profile makes it another candidate drug for controlled studies in CP. The IV drugs lidocaine, propofol, and ketamine have shown efficacy in placebo controlled trials and seem to have a potential for shortterm control of CP [50-52]. Their effects give interesting insights into the etiology of CP and into the biochemical basis of the disorder, but their form of application and their potential side effects make them unsuitable for long-term treatment on a routine basis. The same is true for intrathecal baclofen [53].

The search for a better treatment of CP should be an urgent priority. From the clinical point of view, it should focus on drugs with more favorable safety profiles than the membrane-stabilizing agents currently used in combination with amitriptyline. It should allow for combination therapy and should answer the question of whether preemptive treatment to reduce the incidence of CP can be recommended, analogous to the prevention of postherpetic neuralgia [54,55].

6.2. Non-pharmacological treatment

Invasive motor cortex simulation, deep brain stimulation (DBS), repetitive transcranial magnetic stimulation (rTMS), and vestibulocochlear stimulation have been tried in patients with CPSP refractory to pharmacotherapy. Cortical simulation for relieving chronic pain was noted during epilepsy surgery by Penfield and Jasper who observed relief of burning pain after resection of the contralateral postcentral gyrus. Recurrence of pain subsided after resection of the contralateral precentral gyrus [56].

Electrical stimulation of the prefrontal cortex resulted in significant alleviation of nociceptive response latency in experimental animals [57]. Epidural motor cortex stimulation is a less invasive method for central deafferentation pain [58]. Motor cortex stimulation activates the intercortical interneurons rather than the corticospinal axons. Stimulation of these neurons affects different areas such as thalamocortical projections from ventro-lateral and ventro-anterior thalamus, collaterals of corticocortical projections, especially in premotor and post central cortex, and local cortical connections parallel to cortical layers. Both orthodromic and antidromic propagation of these stimuli result in a cascade of events which modulate neuronal networks of the limbic system, thalamus, and brainstem [59-62]. Motor cortex stimulation has also been shown to increase noradrenergic activity and increased release of endogenous morphine [63,64].

7. Conclusion

Pain problems associated with lesion, disorder or dysfunction of the CNS are a common and prominent problem. As suggested by Beric, there is likely a number of different CP problems but it is as yet unclear how similar or dissimilar the clinical presentations may be nor whether there are different underlying neurobiologic mechanisms [65]. Further studies associating clinical presentation with neurobiologic mechanisms are needed. This will hopefully generate more effective treatments. Further study is also needed concerning how patients cope with pain problems and whether there are any behavioral vulnerability factors.

Finally, whereas impaired pain perception or decreased response to noxious stimuli may not be as problematic as CP, this may be of concern and is deserving of further study.

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Sažetak

Centralna bol: mehanizmi, semiologija i terapija

Bol koja je posljedica oštećenja ili poremećaja funkcije centralnog živčanog sustava čest je problem u svakodnevnoj praksi. Cilj ovog istraživanja bio je prikupiti rezultate dosadašnjih studija vezane uz ovu tematiku te prikazati etiologiju, patogenezu, kliničku prezentaciju i mogućnosti liječenja centralne boli. Osobita pažnja posvećena je moždanom udaru kao uzroku centralne boli. Općenito, etiologija i patofiziologija centralne boli slabo je istražena, a liječenje je dugotrajno i najčeće slabih rezultata. U najvećem broju slučajeva, centralnu bol nije moguće u potpunosti izliječiti, može se samo djelomično ublažiti. Od metoda liječenja najčešće se koriste antidepresivi, antiepileptici te stimulacija motoričkog korteksa. Kirurške metode liječenja se rijetko koriste jer nisu dugotrajne, njima se centralna bol može samo nakratko ukloniti. Za sada ne postoje jasne kliničke smjernice za liječenje centralne boli, postoje samo sporadične studije o liječenju iste što je vjerojatno posljedica nedovoljnog poznavanja etiologije i patogeneze centralne boli te je u tu svrhu potrebno planirati daljnja istraživanja.

Ključne riječi: centralna bol; etiologija; liječenje.