Chronic Pain of Central Origin

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KEY POINTS

- Definition & Classification: Chronic central neuropathic pain arises from lesions or diseases of the central somatosensory nervous system, including stroke, spinal cord injury (SCI), brain injury, and multiple sclerosis (MS).
- Clinical Presentation: Common symptoms include burning pain, allodynia, hyperalgesia, and dysesthesia, often affecting the contralateral side of a central lesion.
- Diagnosis: It is often a diagnosis of exclusion, relying on patient history, somatosensory examinations, and neuroimaging (magnetic resonance imaging [MRI], computed tomography [CT], electroencephalogram [EEG], somatosensory evoked potential [SEP]).
- Treatment Approaches: Includes pharmacological (tricyclic antidepressants (TCAs), gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), opioids in refractory cases), interventional (spinal cord stimulation, neuroablation, nerve blocks), and nonpharmacological (cognitive behavioral therapy (CBT), transcutaneous electrical nerve stimulation (TENS), physiotherapy).
- Challenges & Future Directions: Pain management is complex due to psychosocial factors, opioid misuse risks, and treatment resistance, requiring multidisciplinary approaches and ongoing research into neurophysiological mechanisms.

INTRODUCTION

Chronic central neuropathic pain is defined as a long-standing pain arising as a direct consequence of a lesion or disease affecting the central somatosensory nervous system. Etiologies include vascular events (e.g., stroke), traumatic injuries (e.g., spinal cord or brain injury), and neurodegenerative conditions such as multiple sclerosis (MS). Although neuropathic pain in general is estimated to affect 7%–10% of the global population, the prevalence of centrally mediated pain remains difficult to ascertain due to its diagnosis-by-exclusion nature and variable clinical presentation.[1]

The negative impact of central pain on psychological well-being—including heightened risks of anxiety, depression, and sleep disturbances—underscores its clinical relevance.[2]

It is essential, particularly for anaesthesiology trainees and pain specialists, to understand not only the mechanisms underlying this condition but also the wide range of management modalities that can be employed to improve patient outcomes.

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CLASSIFICATION OF CHRONIC CENTRAL NEUROPATHIC PAIN

Chronic central neuropathic pain can be classified into several subtypes based on its underlying etiology:

- ***Chronic Central Poststroke Pain (CPSP)*:** Typically affects patients after a stroke, with thalamic involvement being especially predictive. Approximately 11% of stroke patients develop CPSP, and nearly 50% of those with thalamic strokes experience such pain, often emerging within the first month; however, symptoms may also appear up to 6 years poststroke.[3,4]
- ***Chronic Central Neuropathic Pain Associated with Spinal Cord Injury (SCI)*:** This subtype follows lesions affecting the somatosensory pathways within the spinal cord and is reported to occur in 40%–70% of SCI patients.[1]
- ***Chronic Central Neuropathic Pain Associated with Brain Injury*:** Resulting from damage to the somatosensory areas of the brain, this pain most often manifests as headache with prevalence figures varying between 106 and 600 per 100,000.[1]
- ***Chronic Central Neuropathic Pain Associated with Multiple Sclerosis (MS)*:** Demyelination within the central nervous system in MS patients disrupts pain signalling, with about 23% of these patients suffering from neuropathic pain.[1]

CLINICAL PRESENTATION AND PATHOPHYSIOLOGY

Symptomatology

Chronic pain of central origin is usually described as burning, aching, squeezing, or pricking and is frequently accompanied by sensory impairments such as allodynia and/or hyperalgesia.[2] In addition, sensory disturbances (e.g., dysesthesia) complicate the clinical picture and may fluctuate over time.

Pain distribution is also influenced by etiology and the location of the sensory-motor defects.[5] Patients with brainstem lesions may exhibit 'crossed signs': damage to the ascending spinothalamic tract results in contralateral hemibody pain, whereas involvement of brainstem nuclei may cause ipsilateral facial pain. MS may cause trigeminal neuralgia secondary to brainstem lesions causing bilateral facial pain.[6]

Central neuropathic pain resulting from spinal cord injury may manifest as segmental pain or pain below the spinal lesion, in contrast with pain resulting from damage at supraspinal levels, which results in a pain distribution contralateral to the lesion site.[6]

Pathophysiology

The International Association for the Study of Pain has defined central post-stroke pain as 'the pain originating as a direct consequence of a lesion or disease that may affect the central somatosensory functions.[2]

The mechanisms underlying chronic central pain involve:

- **Disinhibition and Cortical Hyperexcitability:** Stroke-induced injury, particularly to the lateral thalamus, can cause disinhibition of GABAergic neurons within the ventral posterolateral nucleus. This disinhibition leads to increased activity in cortical areas, which in turn contributes to the manifestation of pain.
- **Temperature and Sensation Alterations:** Cold allodynia is postulated to result from disinhibition of temperature-sensitive fibres, particularly those responsible for detecting cold stimuli.[2,4] Hypersensitivity can be explained as arising from the denervation of existing neurons of the spinothalamic tract post-injury.[2]
- **Central Sensitization:** In 2017, the International Association for the Study of Pain redefined central sensitization under the broader term "nociplastic pain," emphasizing pain that persists for more than 3 months without clear evidence of ongoing tissue damage or neuropathic injury.[2]
  Inflammatory mediators and deafferentation in thalamocortical regions further contribute to the complex sensory abnormalities seen in chronic central pain.

DIAGNOSTIC APPROACH

Given its heterogeneous presentation, diagnosing chronic central neuropathic pain requires a comprehensive clinical evaluation that includes:

- **Detailed Medical History and Patient Interview:** Emphasis is placed on the timing of symptom onset relative to the inciting central lesion and excluding other causes of pain.
- **Somatosensory Examination:** Testing for thermal and tactile hypersensitivities, as well as comparisons between contralateral and ipsilateral sensations, is critical.
  Partial or complete aberrations in pinprick and temperature sensation are often observed with patients while their proprioception and vibration sensation remain intact.[2]

- **Neuroimaging:** Advanced imaging modalities (MRI, CT) are used to correlate clinical findings with structural lesions. In addition, neurophysiological tests such as electroencephalogram (EEG) and somatosensory-evoked potentials (SEP) may aid in substantiating the diagnosis.[2,4]

The diagnosis of central pain is largely one of exclusion, necessitating the careful differentiation from peripheral neuropathic processes.[2]

Comorbidities such as depression and anxiety often coexist with chronic central pain, complicating its management.

MANAGEMENT STRATEGIES

Management of chronic central neuropathic pain is challenging and typically requires an individualized, multidisciplinary approach involving pharmacological, interventional, and nonpharmacological techniques.

1. Pharmacological Treatments

- **First-Line Agents:** Tricyclic antidepressants (TCAs), particularly amitriptyline (administered at approximately 75 mg/d), are considered first-line therapy for CPSP, with careful cardiovascular monitoring required in elderly patients due to adverse effects such as orthostatic hypotension and cardiac arrhythmia.[2]
- **Adjunctive and Second-Line Agents:** Gabapentinoids (gabapentin and pregabalin) and SNRIs provide additional pain relief. Combination therapies may allow for reduced dosages of individual medications, thereby minimizing adverse effects.[2] Tramadol is another agent with proven central effects, although opioids are generally reserved for refractory cases due to the risk of dependence.
- **Third-line Agents:** Other medications, including opioids (e.g., morphine) or opioid antagonist (e.g., naloxone), as well as medical cannabinoids, beta blockers, and sodium-channel blockers (e.g., mexiletine), can be individually recommended. Intravenous medications such as ketamine and opioids could be considered for administration as an ultimate step in a hospital setting, provided the pain does not respond to other therapeutic agents.[2]

2. Interventional Approaches

For patients who do not respond to conservative treatments, interventional therapies may be considered:

- **Neurostimulatory Techniques:** Techniques such as repetitive transcranial magnetic stimulation (rTMS), motor cortex stimulation, and deep brain stimulation (DBS) have shown promise in reducing pain intensity in chronic central pain syndromes.[5,6]
- **Minimally Invasive Procedures:** Procedures including nerve blocks, epidural steroid injections, and radiofrequency neuroablation may be appropriate based on the patient's symptom profile.
  Administration of baclofen can be considered in the cases with other poststroke symptoms including pain related to spasticity.[4]

3. Nonpharmacological Approaches

- **Physical Therapies:** Modalities such as TENS and acupuncture may provide temporary pain relief.
- **Psychological Interventions:** CBT is instrumental in addressing the psychological sequelae, such as anxiety and depression that often accompany chronic pain.[1]
- **Rehabilitation:** Occupational and physical therapy contribute to functional recovery and help manage secondary musculoskeletal issues.[2]
- **Neurofeedback and virtual reality:** New methods such as EEG neurofeedback may be effective in reducing central neuropathic pain in individuals with spinal cord injury and traumatic brain injury as show across six small single-arm studies. However, randomized controlled trials with large sample sizes are still needed to provide high-quality evidence for this treatment modality. Virtual reality interventions, which are commonly used to deliver sensorimotor rehabilitation in individuals with central nervous system injuries, could also be beneficial in decreasing central neuropathic pain after spinal cord injury, as evidence suggests.[7]

5. CHALLENGES IN MANAGEMENT

Management is complicated by the following factors:

- **Difficult diagnosis:** More research is needed to establish reliable diagnostic, prognostic, predictive and response biomarkers to improve clinical practice and trial design.[7]
- **Better understanding of neurophysiological mechanisms:** Clinical applications of neuromodulatory techniques depend on the understanding of relationship between neurophysiological effects and functional outcomes for the development of patient-tailored stimulation protocols that encompass long-term effectiveness and safety data.[6]

- **Inadequate Pain Relief:** The inherent resistance of central pain to traditional pain medications often results in suboptimal outcomes.
- **Psychosocial Comorbidities:** High rates of anxiety, depression, and sleep disturbances can worsen overall patient prognosis. Also, the extent of recovery from the pain symptoms seems to be moderate[8], associated with cognitive decline, and increased functional dependence, further impacting the management of this type of chronic pain.[8]
- **Opioid Misuse Risk:** Despite opioids having limited efficacy for central pain their potential for misuse remains a significant concern.
- **Need for Multidisciplinary Care:** Optimal management necessitates the coordinated efforts of neurologists, physiatrists, psychologists, and pain specialists.

FUTURE DIRECTIONS

Continued research is essential to elucidate the neurophysiological mechanisms underlying chronic central neuropathic pain. Future studies should focus on:

- Identification of novel molecular targets.
- Optimization of interventional therapies.
- Longitudinal assessments of combined pharmacologic and nonpharmacologic protocols.
- Strategies to better manage the psychosocial dimensions of chronic pain.

SUMMARY

Chronic pain of central origin is characterized by diverse clinical manifestations and intricate pathophysiological mechanisms. Chronic pain of central origin poses significant diagnostic and therapeutic challenges. Although current treatment modalities including TCAs, gabapentinoids, neurostimulatory techniques, and CBT offer varying degrees of benefit, a single therapeutic approach is rarely sufficient. A comprehensive, patient-centered, and multidisciplinary management plan is imperative, and ongoing research into central pain mechanisms holds promise for improved future outcomes.

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