
Central Poststroke Pain: Current Diagnosis and Treatment

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Central post-stroke pain syndrome (CPSP) is a debilitating sequel that can follow thalamic sensory stroke. Less well recognized, CPSP follows lateral medullary stroke and parietal cortical stroke and may develop anywhere along the spinothalamic or trigemino-thalamic pathways. Patients describe sharp, stabbing, or burning pain and experience hyperpathia and especially allodynia. Although CPSP was first described over 100 years ago, CPSP is too frequently under-recognized. It is treatable disorder. Pharmacological therapy, magnetic stimulation, and invasive electrical stimulation are reviewed and recommendations made. **Key words:** *central post-stroke pain, cortical pain, deep brain stimulation (DBS), lateral medullary stroke, pharmacotherapy, repetitive transcortical magnetic stimulation (rTMS), thalamic pain*

Although pain associated with sensory deficits following otherwise minor stroke has been recognized for over 100 years, it remains a clinically challenging problem today, posing difficulties both in recognition and therapy. Two of our recent cases illustrate this.

Case 1

A 60-year-old woman with a past history of stroke, hypertension, diabetes, dyslipidemia, and depression was evaluated for the complaint of not remembering the names of her children. During her evaluation, it was discovered that she had intermittent right arm pain, right perioral numbness, and involuntary movements of the right hand and forearm. Exam demonstrated decreased sensitivity to pinprick involving the right upper extremity as well as postural tremor of the right upper extremity and chorea of the right hand and forearm, mild flattening of the nasolabial fold on the right, and dyskinesic tongue movements. Among her many problems, including poststroke depression, Dejerine-Roussy syndrome was suspected. MRI brain was obtained confirming a chronic right thalamic infarct (**Figure 1**). The patient responded well to duloxetine 60 mg daily and counseling regarding her right-sided dysesthesias and abnormal movements.

Case 2

A 56-year-old right-handed man with a past medical history including brainstem infarction 8 years prior presented with severe left facial pain thought to represent long-standing trigeminal neuralgia.

Examination demonstrated decreased pinprick and temperature sensibility involving the right hemibody with right facial sensation apparently intact. The presence of allodynia was demonstrated by an unpleasant sensation triggered by soft touch to the left face. Exam also demonstrated decreased vibratory sensitivity bilaterally in distal lower extremities, wide-based gait, and very poor tandem gait.

His medical history included mild residual ataxia, dysphagia, and vocal cord weakness following left lateral medullary and left cerebellar stroke 8 years earlier, type II diabetes diagnosed at the time of his stroke, obesity, hyperlipidemia, obstructive sleep apnea, gastroesophageal reflux, and most recently essential thrombocythemia. An earlier tentative diagnosis of antiphospholipid antibody syndrome could not be substantiated. His medications at

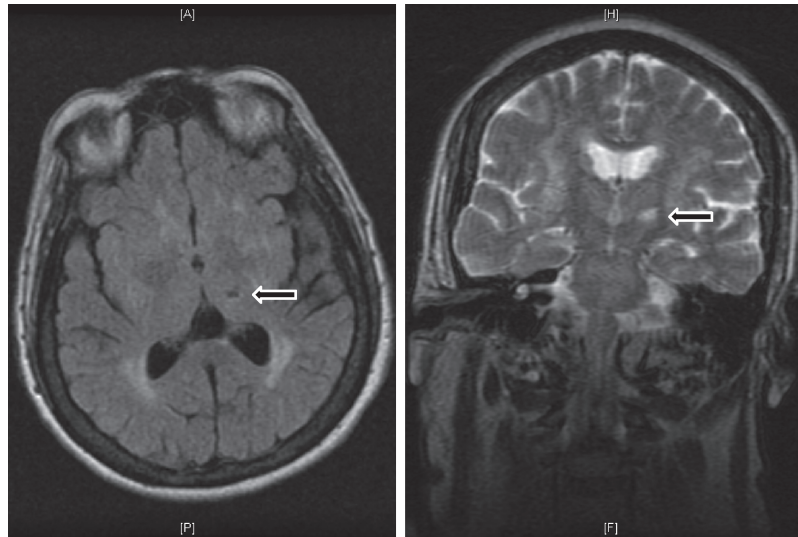


Figure 1. Axial T2 FLAIR MR image (left panel) showing a chronic left thalamic infarction (arrow). A T2 coronal image (right panel) demonstrates the postero-lateral thalamic location of the infarct.

evaluation included acetaminophen, escitalopram, hydroxyurea, lansoprazole, metformin, nortriptyline, oxcarbazepine, saxagliptin HCl, and tramadol. MRI brain demonstrated the old left lateral medulla ischemic infarction (**Figure 2**).

His left facial pain was attributed to central poststroke pain syndrome (CPSP). Oxcarbazepine and escitalopram were discontinued while nortriptyline was increased to 100 mg nightly and gabapentin was initiated at 300 mg at bedtime and gradually advanced to 300 mg 3 times daily. He enjoyed a marked decrease in facial discomfort over subsequent weeks.

CPSP: Definition, History, and Diagnosis

Neuropathic (or neurogenic) pain arises not from the normal signaling functions of nociceptors, but from abnormal pain signaling within the nervous system. Central pain is a form of neuropathic pain caused by damage or dysfunction within the central nervous system. CPSP is defined as a central pain syndrome occurring as a direct consequence of a cerebrovascular lesion, most commonly ischemic stroke but also hemorrhagic stroke, associated with either intracerebral or subarachnoid bleeds.¹

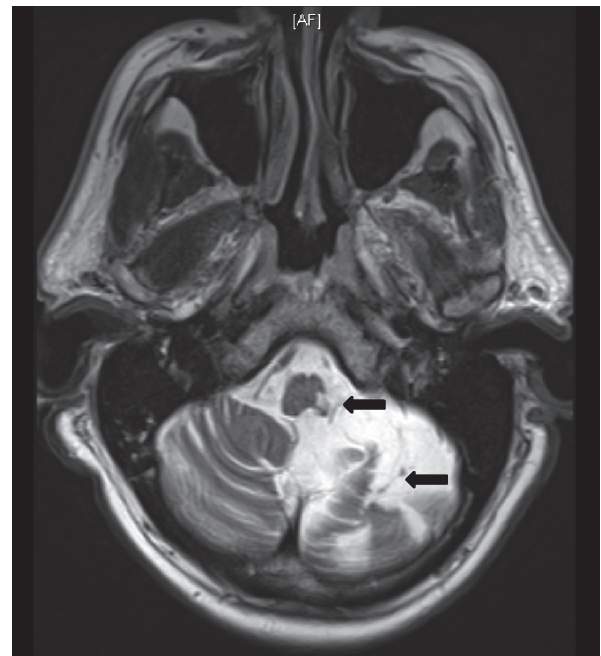


Figure 2. T2 weighted MR image showing a chronic left lateral medullary plate lesion (upper arrow) and a posterior inferior cerebellar artery infarct of the same age (lower arrow).

In some instances, pain is present at stroke onset, but this is not common. CPSP typically begins days or weeks after the ictus. In a

prospective study, 63% of patients were affected within 1 month, another 18% within 6 months, and the remaining 18% after 6 months.² CPSP is characterized by disabling chronic pain and sensory abnormalities. Individuals suffer from pain described as mild to moderate, recurrent or constant, sharp, stabbing, burning, or paradoxically burning cold. Patients further describe the pain as “troublesome, annoying or tiring.”¹ Pain is always or nearly always circumscribed within an area of stroke-associated sensory deficit involving pinprick or thermal sensation.³ Patients describe spontaneous pain and pain evoked by touch or movement. Undue sensitivity to noxious stimuli (hyperpathia) may be present. Spontaneous unpleasant sensations (dysesthesias) may be present. Allodynia, an exaggerated response to normal touch or another normally nonpainful stimulus perceived as intense pain, may be present. Allodynia may involve single modalities such as warmth, coolness, or soft touch or more complex stimuli such as a moving brush termed mechanical allodynia.⁴ Mechanical allodynia in response to contact with clothing, bed sheets, or air currents can be particularly debilitating. Allodynia, when present, is pathognomonic of neuropathic pain and is a common feature in patients with CPSP; it is reported in two-thirds of CPSP patients and in more than 90% of patients in selected series.³ CPSP is a major impediment to stroke recovery, causing difficulties during rehabilitation and interfering with sleep. In some cases, it is associated with self-harm.¹

The history of CPSP begins with the description of the “thalamic syndrome” by Dejerine and Roussy in 1906.⁵ Such patients tended to have hemibody sensory deficits, mild motor deficits often associated with abnormal movements or posturing and minor stroke overall. Although thalamic lesions comprise only 1 of the 3 anatomical locations commonly associated with CPSP, it remains the best known. Head and Holmes⁶ described patients with cortical lesions and central pain in 1911; subsequently, lateral medullary lesions and pontine lesions were added, leading to the generalization that lesions anywhere along the spinothalamic tract or its trigeminal equivalent could cause central pain.³

Currently, it is generally recognized that injury to the spinothalamic tract or its central targets is necessary but not sufficient for the formation of CPSP. It is unclear how a secondary pathologic gain of function then develops.¹ The anatomic fine structure of lesions crucial to the formation of thalamic pain involves circumscribed areas of the ventral and lateral thalamus, but the precise fine structure is still debated.^{7,8} CPSP of cortical origin seems to involve an increasingly well-defined anatomical region in the posterior insula and neighboring opercular parietal cortex.⁹

Poststroke pain is common in stroke survivors. CPSP is not uncommon. In a population-based study of stroke patients, prevalence of CPSP is 8% but may range from 1% to 12% in different series.¹⁰ Frequency of CPSP appears to depend upon lesion location. In lateral medullary infarction (Wallenberg’s), 25% of cases may develop CPSP; in inferior-lateral thalamic infarctions, 17% to 18% of cases go on to develop CPSP.^{1,11} Cortically based CPSP seems less frequent and involves the posterior insular and adjacent parietal cortex most specifically.⁹

Although the diagnosis of CPSP is too frequently overlooked, it is crucial that the clinician carefully consider other causes of poststroke pain. Musculoskeletal pain, especially pain related to abnormal shoulder movement, is probably most common and comprises roughly 40% of cases; headache following stroke is common, and pain associated with spasticity must also be considered.¹ Finally, the clinician should recognize that several types of chronic pain often co-occur in patients, and the contribution of each type needs to be differentiated at the initiation of treatment and as treatment proceeds.

Pharmacological Treatment

Clinical data regarding pharmacological treatment are limited both by the small numbers of patients enrolled and by a lack of well-designed trials. We calculate that up to 2009, a total of 96 CPSP patients were involved in 6 randomized controlled trials (RCTs) or masked outcome trials (Class IIB or better) as listed in a systematic review by Kumar and colleagues.¹¹ What we believe to

be the largest RCT to date, published in 2011,¹² included 219 patients and failed with regard to the primary endpoint, which was adequate improvement in pain scales in patients treated with pregabalin.

Medications from the following groups can be considered: antidepressants, anticonvulsants, antispasticity drugs, anesthetic agents, and analgesics.

Antidepressants

Tricyclic antidepressants

Amitriptyline is considered to be the first-line treatment for CPSP, however side effects may be an issue and not all patients respond to amitriptyline.¹³ Placebo-controlled studies show efficacy in treating CPSP.^{14–16} Anti-cholinergic side effects include dry mouth, constipation, and urinary retention. Orthostatic hypotension and cardiac arrhythmia are potentially serious side effects. Other tricyclic antidepressants (TCAs) such as nortriptyline are known to treat other forms of neuropathic pain,¹⁷ but their efficacy in patients with CPSP remains to be clearly established.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have less serious side effects than TCAs, but there are no placebo-controlled studies confirming their efficacy for CPSP.¹⁵ Fluoxetine, up to 125 mg daily, was effective in patients with CPSP who had stroke within 1 year.¹⁸ In that study, effectiveness of pain treatment seemed independent of effect on depression.

Selective serotonin and norepinephrine reuptake inhibitors

Dual-action antidepressants are known to be effective in different chronic pain syndromes. These agents increase the availability of the neurotransmitters serotonin and norepinephrine and generally have relatively fewer side effects than TCAs. Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) currently available in the United States are

venlafaxine, duloxetine, and desvenlafaxine. Milnacipran is approved in Europe for depression and is approved in the United States for fibromyalgia. Venlafaxine, milnacipran, and duloxetine may be more effective in relieving pain than SSRIs.¹⁹ Multiple studies report the efficacy of SNRIs in neuropathic pain syndromes,^{20–26} but as of yet there are no specific studies limited to CPSP.

Commonly used anticonvulsants

Agents initially developed as anticonvulsants make attractive candidates for possible efficacy in neuropathic pain syndromes generally and in central pain syndromes in particular. Several anticonvulsant agents are used in the treatment of CPSP, but there have been only a few controlled clinical studies.

Carbamazepine

In a placebo-controlled, crossover study comparing amitriptyline, carbamazepine, and placebo, carbamazepine was better at 3 weeks only, whereas amitriptyline was significantly better than placebo in relieving pain at 2, 3, and 4 weeks.¹⁴ Carbamazepine, particularly at higher plasma levels, has been found to be beneficial.¹³ Use of carbamazepine is limited by its side-effect profile and interaction with other medications. Clinicians should be aware of ataxia, rash, hyponatremia, bone marrow dysfunction, and hepatic dysfunction as possible side effects. Overall, the efficacy of carbamazepine is limited.¹¹

Lamotrigine

Lamotrigine monotherapy was found to be moderately effective in amounts up to 200 mg/day in randomized double-blinded placebo-controlled trial of 27 CPSP patients.²⁷ At the maximum tested dose, 200 mg daily, pain reduction appeared clinically meaningful and statistically significant when compared to controls. Lamotrigine was well tolerated except for the occurrence of mild rash. However, Stevens-Johnson syndrome and toxic epidermal necrolysis (TENS) are serious potential

side effects of lamotrigine, and appropriate patient instruction must be given.

Gabapentin

Gabapentin has proved to be efficacious and well tolerated in other neuropathic pain syndromes such as diabetic neuropathy.²⁸ Gabapentin is relatively tolerable, safe, and has minimal interactions with other drugs.¹³ The starting dose of gabapentin generally is 300 mg 3 times daily for 3 days, gradually increasing to 1800 or 2400 mg daily. A few patients encounter undue somnolence at the usual starting dose, and therapy in these cases can be reinitiated at 100 mg 3 times daily.

Anesthetics

Ketamine

Ketamine may have a role in refractory patients with CPSP.²⁹

Lidocaine

In a randomized, double-blind, placebo-controlled trial of 16 patients with neuropathic pain receiving lidocaine, a majority of patients (62.5%) had significant relief of spontaneous pain.³⁰

Antispasticity drugs

Baclofen

Studies are lacking, but there have been reports on the use of baclofen for neuropathic central pain syndrome or complex regional pain syndrome (reflex sympathetic dystrophy).³¹

Newer or less commonly used anticonvulsants

Pregabalin is approved for fibromyalgia. In a study of patients with central neuropathic pain caused by brain or spinal cord injuries, there was overall improvement in patients suffering from severe central pain.^{13,32–34}

Levetiracetam³⁵ and oxcarbazepine³⁶ are known to reduce neuropathic pain, although studies in poststroke pain are lacking. There is inconclusive

evidence supporting the use of phenytoin, zonisamide, and topiramate in CPSP.

Overall, there are few options. Amitriptyline and lamotrigine can be considered first-line agents and gabapentin is considered a second-line drug.¹¹ Polypharmacy is an option but has little formal trial support. Analgesics are too often ineffective and habituating. In patients not responding to medications, repetitive transcranial magnetic stimulation and deep brain stimulation have been beneficial.¹¹

Nonpharmacological Treatment

Invasive motor cortex stimulation (MCS), deep brain stimulation (DBS), and repetitive transcranial magnetic stimulation (rTMS) are experimental modalities that have been employed in patients with CPSP refractory to pharmacotherapy. The numbers of treated patients are often small. Furthermore, invasive methods tend to limit study design to observation alone, because it is difficult to provide effective controls.

Deep brain stimulation

DBS is a neurosurgical procedure involving insertion of deep stimulating electrodes through burr holes into target brain regions. Once the DBS electrodes are optimally positioned, they are coupled to a pulse generator (pacer) that allows adjustment of pulse frequency, amplitude, and contour. DBS is used to treat Parkinson's disease, depression, and chronic pain. In patients with chronic pain, target structures include periaqueductal or peri-third ventricular gray matter or sensory thalamus. The mechanism of action by which DBS achieves pain relief is not completely understood. In a meta-analysis, DBS was well tolerated and effective in patients with neuropathic pain, although it appeared to be significantly more effective in relieving chronic nociceptive (non-neuropathic) pain. Of the 45 CPSP patients included, 53% of cases achieved sufficient pain relief to justify permanent implantation while 58% of permanently implanted patients maintained pain relief at follow-up.³⁷ In a recent series of 15 patients with CPSP, 12 (80%)

achieved sufficient pain relief to justify permanent DBS implantation; of these, 7 patients (58%) had prolonged pain relief sufficient to discontinue all pain medications.³⁸

Epidural stimulation of motor cortex

Pioneered in 1991,³⁹ electrical MCS by means of implanted prefrontal epidural electrodes has been tested in patients with neuropathic pain syndromes of multiple causes. A recent systematic review of 327 patients receiving invasive MCS, including 193 patients with CPSP, found a mean positive response rate of 64% across studies. In follow-up, the mean response rate fell to 55%.⁴⁰ Although these results are encouraging, these studies were neither blinded nor controlled, and the definition of a positive response was set within each individual study and not necessarily standardized.

Repetitive transcranial magnetic stimulation

rTMS is a noninvasive procedure where an external magnetic coil positioned tangentially to the scalp generates a brief high-intensity magnetic field in subjacent brain, inducing an electrical field perpendicular to the magnetic vector. The electrical field may stimulate neurons directly or through induced extracellular currents.⁴¹ The magnetic coil can be positioned over any area of cerebral cortex including the prefrontal cortex. Deliberate misalignment of the coil permits sham stimulation. rTMS appears to be safe and is US Food and Drug Administration (FDA) approved for the treatment of depression. rTMS can be effective for some patients with neuropathic pain. The mechanism of action of rTMS in chronic neuropathic pain is unclear. It may relate to activation of presumably inhibitory projections from the motor and premotor cortices to sensory thalamic nuclei and from there to other deep structures such as brainstem or limbic system.⁴⁰ In one study of 48 patients with neuropathic pain, including 24 with CPSP, rTMS produced a significant decrease in pain compared with controls ($P = .025$). There were no major side effects.⁴² In another randomized controlled study

of rTMS, 24 of 60 patients with neuropathic pain had CPSP. Real stimulation compared with sham stimulation led to pain reduction.⁴³ rTMS of the precentral gyrus (5 or 10 Hz) reduced intractable deafferentation pain in patients with spinal cord injury.⁴⁴ In another study of patients with spinal cord injury, pain reduction in the real rTMS group continued during the follow-up period.⁴⁵ A meta-analysis comparing noninvasive to invasive MCS⁴⁰ found noninvasive MCS using either rTMS or direct current stimulation less effective than invasive MCS, with a responder rate of 40% compared to the 64% reported in the invasive stimulation group. Still, the presence of sham controls enhances the credibility of the rTMS results. In this pooled analysis, there were 274 chronic neuropathic pain patients, including 134 with CPSP.

Conclusions

There are many causes of poststroke pain, and these frequently coexist in our patients. It is crucial to recognize CPSP and differentiate it from musculoskeletal pain or spasticity-associated pain. As our clinical cases illustrate, CPSP can be overlooked. CPSP associated with thalamic stroke is probably best known and therefore more frequently suspected. The pathophysiological insight that CPSP can involve any point along the spinothalamic or trigemino-thalamic pathway is not just mechanistically interesting but clinically useful. The most frequent extrathalamic locus is the lateral medulla and the least recognized common site may be the parietal-insular cortex. With these 3 loci in mind, few cases should be overlooked. CPSP is treatable. Recognition of the syndrome in and of itself can be reassuring to the patient. Amitriptyline and lamotrigine are currently first-line agents, and gabapentin is a second-line agent in common clinical practice. Polypharmacy, although not verified in clinical trials, is probably frequently employed and may be effective. Noninvasive stimulation therapy should be considered in patients who are refractory to pharmacotherapy, and invasive stimulation should certainly be considered in carefully selected patients who are refractory to other approaches.

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