How “Central” is Central Post-Stroke Pain?

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Disclosure

- None
Learning Objectives

- List the leading causes of pain after stroke.
- Review the diagnostic criteria for central post stroke pain.
- Describe the proposed mechanisms for central post stroke pain.
- Identify a plan for medical and non-medical management for CPSP.

Outline

- Introduction
- Epidemiology
- Clinical Presentation
- Proposed Mechanisms
- Management
- Conclusion
Central Neuropathic Pain

Common Causes:
- Ischemic/hemorrhagic stroke
- Multiple sclerosis
- Spinal cord injury
- Syringomyelia
- Vascular malformations
- Infections
- Traumatic brain injury
- Parkinson’s disease?

Lancet Neurol 2009; 8: 857–68

Epidemiology

- Annually, 500,000 people in the US have a first stroke
- 200,000 have a recurrent stroke
- 80% of strokes are ischemic, either thrombotic or embolic in origin
- 5 million people in the US have had a stroke & are living in the community setting
- Of these, 1.1 million have limitations in their daily functioning or ability to perform activities of daily living
- 100,000 people have stroke as their primary diagnosis & are receiving in home health care
**Introduction**

- Pain is among the most common complications of stroke, with reported prevalence of 39% to 55%.
- The leading types of post-stroke pain are headaches, shoulder pain, spasticity, and central post-stroke pain (CPSP).
- Central post-stroke pain is a neuropathic pain disorder caused by the stroke-related lesion affecting the central somatosensory pathways, and accounts for about 25% of post-stroke pain cases.

**CPSP**

- First introduced in 1891 by Edinger.
- In 1906, Déjerine and Roussy provided descriptions of CPSP in 8 pts.
- Further described by Head and Holmes in 1911 describing sensory deficits and pain narratives.
- Riddoch described symptoms of both thalamic and extra-thalamic origin (1938).

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**Time Course**

- Variable
- Can develop immediately after stroke in some patients and up to years later in others.
- Onset can be delayed, but development of CPSP within the first few months is most common.
- In a prospective study that included 16 patients with CPSP, pain onset occurred within the first month after stroke in ten patients, between 1 and 6 months in three patients, and after 6 months in three patients.
- Any later onset of pain should prompt an examination for other causes, such as a new stroke.
- Gradual onset of pain is most common.

*Lancet Neurol* 2009; 8: 857–68
Diagnostic Criteria

- Mandatory criteria
  - Pain within an area of the body corresponding to the lesion of the CNS.
  - History suggestive of a stroke and onset of pain at or after stroke onset.
  - Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion.
  - Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely.

- Supportive criteria
  - No primary relation to movement, inflammation, or other local tissue damage.
  - Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply.
  - Allodynia or dysesthesia to touch or cold.

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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.

Diagnostic Measures

- Pain scales:
  - VAS or NRS are useful in the evaluation of the pain intensity, but there are no scales developed specifically for CPSP.
- Quantitative Sensory Testing (QST):
  - Have been used to document common or dissociated sensory findings.
  - Enable detailed sensory testing of controlled and graded physiological stimuli, such as thermal, pressure, pinprick, and vibration stimuli.

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Clinical Characteristics

- Pain can be spontaneous or evoked.
- Spontaneous is common and reported in 85% of patients.
- On NRS scale, the mean varies between 3-6/10.
- Symptoms and severity in thalamic versus extrathalamic stroke does not differ.
- Intensity can be increased by internal or external stimuli.

Spontaneous Pain Descriptions

- **Continuous:**
  - Burning
  - Aching
  - Pricking
  - Freezing
  - Squeezing

- **Intermittent:**
  - Lacerating
  - Shooting

**CPSP Can reduce quality of life:**
- Can compromise rehabilitation.
- Interfere with sleep.
- Lead to self-mutilation.
- Even push patients to suicide.

Pain Distribution

- Distribution of pain can range from a small area (eg, the hand) to large areas (eg, to one side of the body).
- Large areas are most commonly affected, with or without involvement of the trunk and face.
- In patients with lateral medullary infarction, the pain can involve one side of the face and the contralateral side of the body or limbs, and periorbital pain is frequently reported.
- Hemibody pain is common in patients with thalamic lesions.
Proposed Mechanisms

Loss of STT input to the posterior lateral part of the thalamus causes disinhibition of the medial thalamus leading to pain.

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Proposed Mechanisms

The thermosensory disinhibition theory. A lesion in the lateral cool-signalling spinothalamocortical projections to the thermosensory area of the insula through the posterior part of the ventral medial nucleus causes disinhibition of a medial limbic network involving the parabrachial nucleus and the periaqueductal grey of the brainstem, the medial thalamus, and the ACC.

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A loss of normal inhibition from the rapidly conducting “neospinothalamic” or lateral STT projections causes disinhibition of the slowly conducting polysynaptic paleo spinoreticulothalamic or medial STT projections, resulting in pain.

Deafferentation of ascending pathways to the thalamus might cause central pain due to hyperactive bursting in the thalamus caused by low-threshold calcium spikes.
Proposed Mechanisms

The dynamic reverberation theory. A lesion of the STT causes central pain by creating an imbalance in the normal oscillatory “dialogue” between the cortex and the thalamus.

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Treatments for Central Post Stroke Pain

- Antidepressants
- Anticonvulsants
- Antiarrhythmics
- Opioids
- Steroids
- Intrathecal Baclofen
- Rehab Techniques
- Regional Anesthesia
- Electrical Stimulation
- Deep Brain Stimulation
- Neuroablative Procedures
- Transcranial Magnetic Stimulation
**Antidepressants**

- TCAs are currently viewed as first-line drugs for CPSP.
- Of these, Amitriptyline (75 mg) is considered drug of choice, with consistent relief reported.
- Mild to moderate side-effects were common, particularly lethargy and dry mouth.
- Other TCAs (nortriptyline, imipramine, desipramine) and serotonin/norepinephrine reuptake inhibitors (venlafaxine, duloxetine, milnacipran) have also been reported to be effective, but efficacies have yet to be established.
- Selective serotonin reuptake inhibitors are mostly ineffective.


**Anticonvulsants**

- Gabapentin and pregabalin have well documented efficacy in central neuropathic pain syndromes.
- In a RCT, pregabalin showed a clinically significant effect of treatment on pain levels in patients with central neuropathic pain.
- Most commonly reported side-effects were dizziness, decreased intellectual performance, somnolence, and nausea.

Anticonvulsants

- 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.
- 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.


Anticonvulsants

- 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.
- Use of carbamazepine is limited by its side-effect profile and interaction with other medications.
- Clinicians should be aware of possible ataxia, rash, hyponatremia, bone marrow dysfunction, and hepatic dysfunction.
- Overall, the efficacy of carbamazepine is limited.

Opioids

- Opioids are generally considered ineffective in CPSP.
- However, morphine has been reported to alter significant aspects of pain perception (alldynia and thermal thresholds).
- In one study, morphine appeared to be effective in reducing CPSP because it reduced concurrent nociceptive pain and psychogenic influence.
- Other investigators have reported a loss or inactivation of opioid receptors in the cerebral hemisphere in CPSP, which would explain the low efficacies of opioids and the need for high doses to treat CPSP.
- Opioid treatment is often discontinued because of significant side effects from the high doses necessary for clinical benefit.


Intravenous Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Study Design</th>
<th>Study Size</th>
<th>Dosing Regimen</th>
<th>Outcome Measure</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Ainslie et al. 16</td>
<td>65/65</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>A 2mg/kg IV over 30 minutes</td>
<td>1. Spontaneous pain, VAS 1-100 2. Global assessment of pain relief</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>Cossemi et al. 32</td>
<td>8/8</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>A Single IV bolus of 1.25mg/kg followed by 0.5mg/kg/hr for 120 min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>Bachoura et al. 6</td>
<td>5/5</td>
<td>Double-blind, placebo-controlled, crossover</td>
<td>A 20mg/kg IV over 5 min</td>
<td>Pain rating scale 0-10</td>
<td>Pain relief: &gt; 50% in 97% of patients with CPSP, no difference in patients with CPSP and healthy controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamasato et al. 35</td>
<td>20/20</td>
<td></td>
<td>Uncontrolled trial, not randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Yamasato et al. 36</td>
<td>108/108</td>
<td>Uncontrolled trial, not randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Yamasato et al. 36</td>
<td>108/108</td>
<td>Controlled trial, randomized, placebo-controlled, crossover</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ainslie et al. 16</td>
<td>5/5</td>
<td></td>
<td>Placebo-controlled, crossover</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A: randomized placebo-controlled trial; B: uncontrolled trial; IV: intravenous; d: day; vs: versus; n.s: not significant.

Neurostimulation

□ Motor cortex stimulation:
   – Mechanism not completely understood. However, studies have indicated changes in cerebral blood flow in several areas, including the thalamus, after successful motor cortex stimulation.
   – In two recent reviews, the 1-year success rate in patients with CPSP was concluded to be about 45–50%.
   – Severe complications are rare.
   – Most common complications reported are seizures (intraoperatively or during the trial period), infections, and hardware problems.

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□ Transcranial magnetic stimulation:
   – Non-invasive method.
   – The effects on pain are often modest and short lasting.
   – Adverse events are rare.
   – Recurring sessions of repetitive transcranial magnetic stimulation of the motor cortex have been shown to extend pain relief.
   – The result of this treatment might be a useful predictor for the efficacy of motor cortex stimulation.

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Neurostimulation

- Deep brain stimulation:
  - Main targets are the sensory (ventral posterior) thalamus and the periventricular gray matter.
  - Reported efficacy rates range from 25% to 67%, but with wide ranges of pain relief.

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Neurostimulation

- Vestibular caloric stimulation:
  - Effect probably due to activation of the posterior insula and subsequent inhibition of pain generation in the anterior cingulate.
  - Two small studies:
    - In one study (n=2), CPSP was substantially relieved by VCS.
    - In another study of 9 patients, there was a significant immediate treatment effect for cold-water caloric stimulation.

Neurocase 2007; 13(3): 185-188.
How central is central poststroke pain? The role of afferent input in poststroke neuropathic pain: a prospective, open-label pilot study


Screening Protocol

- 55 pts screened
- 11 pts met screening criteria
- 8 pts included
- 44 pts excluded (anticoagulation, geography, pain severity<4, not interested)
- 2 subsequently excluded because they did not meet definite CPSP criteria, 1 subject withdrew consent, all before any intervention
Demographic Data

Table 1
Demographic data and stroke characteristics.

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age, sex</th>
<th>Race</th>
<th>BMI</th>
<th>Stroke type</th>
<th>Stroke location</th>
<th>Additional details</th>
<th>Time since stroke</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51, F</td>
<td>Black/African heritage</td>
<td>49.2</td>
<td>H</td>
<td>Rt thalamus</td>
<td>Intraventricular extension</td>
<td>6.0 yr</td>
<td>HTN, depression, c/o hysterectomy, dyslipidemia, and DM</td>
</tr>
<tr>
<td>2</td>
<td>47, M</td>
<td>Black/African heritage</td>
<td>37.9</td>
<td>H</td>
<td>Lt basal ganglia and thalamus</td>
<td>Extension into Lt frontal-parietal lobes</td>
<td>6.9 yr</td>
<td>HTN, depression, TIA, CKD, and aneurysm</td>
</tr>
<tr>
<td>3</td>
<td>62, M</td>
<td>Caucasian</td>
<td>29.7</td>
<td>H</td>
<td>Lt basal ganglia and thalamus</td>
<td></td>
<td>1.3 yr</td>
<td>HTN, c/o cholesterol, and c/o hemorrhoidectomy</td>
</tr>
<tr>
<td>4</td>
<td>37, F</td>
<td>Black/African heritage</td>
<td>24.4</td>
<td>H</td>
<td>Rt basal ganglia (h) and Rt medial thalamus (b)</td>
<td>Thalamic ischemic stroke occurred 3 months after hemorrhagic stroke</td>
<td>1.7 yr</td>
<td>HTN, depression, DM, and dyslipidemia</td>
</tr>
<tr>
<td>5</td>
<td>52, F</td>
<td>Caucasian</td>
<td>28.6</td>
<td>I</td>
<td>Rt thalamus</td>
<td></td>
<td>11 mo</td>
<td>HTN, depression, DM, and dyslipidemia</td>
</tr>
<tr>
<td>6</td>
<td>56, M</td>
<td>Black/African heritage</td>
<td>29.0</td>
<td>I</td>
<td>Rt internal capsule</td>
<td></td>
<td>9 mo</td>
<td>HTN and depression</td>
</tr>
<tr>
<td>7</td>
<td>60, M</td>
<td>Black/African heritage</td>
<td>28.0</td>
<td>H</td>
<td>Lt basal ganglia</td>
<td>Extension into Lt caudate, thalamus, and lateral ventricle</td>
<td>2.3 yr</td>
<td>Glaucoma, CAD, CKD, DD, dyslipidemia, and HTN</td>
</tr>
<tr>
<td>8</td>
<td>48, F</td>
<td>Caucasian</td>
<td>21</td>
<td>I</td>
<td>Lt basal ganglia, thalamus, and occipital lobe</td>
<td></td>
<td>4.3 yr</td>
<td>Iron deficiency anemia</td>
</tr>
</tbody>
</table>

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disorder; H, hemorrhagic; HTN, hypertension; I, ischemic; IPH, intraparenchymal hemorrhage; TIA, transient ischemic attack.

Pain Characteristics

Table 2
Central poststroke pain characteristics.

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Pain onset</th>
<th>Pain duration</th>
<th>BPI—pain severity</th>
<th>BPI—pain interference</th>
<th>NPSI total score</th>
<th>Analgesics</th>
<th>Nerve block site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Immediate</td>
<td>&gt;5 yr</td>
<td>6.0</td>
<td>5.4</td>
<td>23</td>
<td>Naproxen and acetaminophen (paracetamol)</td>
<td>Left brachial plexus</td>
</tr>
<tr>
<td>2</td>
<td>Immediate</td>
<td>&gt;5 yr</td>
<td>6.8</td>
<td>2.4</td>
<td>37</td>
<td>None</td>
<td>Left leg (bladder and peroneal nerves)</td>
</tr>
<tr>
<td>3</td>
<td>3-12 months after stroke</td>
<td>6-12 mo</td>
<td>6.0</td>
<td>3.6</td>
<td>49</td>
<td>Tramadol</td>
<td>Right brachial plexus</td>
</tr>
<tr>
<td>4</td>
<td>3-12 months after stroke</td>
<td>6-12 mo</td>
<td>5.8</td>
<td>6.6</td>
<td>26</td>
<td>Gabapentin, NSAIDs, and acetaminophen (paracetamol)</td>
<td>Left brachial plexus</td>
</tr>
<tr>
<td>5</td>
<td>3-12 months after stroke</td>
<td>6-12 mo</td>
<td>8.5</td>
<td>9.6</td>
<td>58</td>
<td>Gabapentin</td>
<td>Left brachial plexus</td>
</tr>
<tr>
<td>6</td>
<td>0-1 month after stroke</td>
<td>6-12 mo</td>
<td>5.0</td>
<td>5.6</td>
<td>26</td>
<td>None</td>
<td>Left leg (bladder and peroneal nerves)</td>
</tr>
<tr>
<td>7</td>
<td>0-1 month after stroke</td>
<td>2-5 yr</td>
<td>7.5</td>
<td>6</td>
<td>60</td>
<td>Gabapentin</td>
<td>Right brachial plexus</td>
</tr>
<tr>
<td>8</td>
<td>Immediate</td>
<td>2-5 yr</td>
<td>4.8</td>
<td>2.7</td>
<td>34</td>
<td>Duloxetine</td>
<td>Right elbow (ulnar, radial, and median nerves)</td>
</tr>
</tbody>
</table>

BPI, Brief Pain Inventory; NPSI, Neuropathic/Pain Symptom Inventory; NSAIDs, nonsteroidal anti-inflammatory drugs.
Regional Block Technique

Pain Distribution

Primary Outcome of Change in Spontaneous Pain

Figure 2. Primary outcome of change in spontaneous pain. Intensity of ongoing pain at baseline (before the block) and 30 minutes after the block (primary outcome). Each subject is coded by a different color. NRS, numerical rating scale.

Individual Pain Scores

Figure 3. Individual pain score changes after the nerve block. After the peripheral nerve blockade, pain intensity returned to baseline within 4 to 7 hours in 4 patients, consistent with the duration of lidocaine action. In 3 patients, pain scores remained zero for 8 hours after the nerve block, in 1 patient (44, baseline NRS = 7), pain intensity remained at NRS = 2. NRS, numerical rating scale.

Intensity scores for thermal and mechanical sensation in the painful extremity.

<table>
<thead>
<tr>
<th>Sensory modality</th>
<th>Baseline</th>
<th>30 minutes after the block</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold</td>
<td>7 (4.5–7.8)*</td>
<td>0 (0.0–1.9)*</td>
<td>0.000</td>
</tr>
<tr>
<td>Heat</td>
<td>5.9 (±1.4)</td>
<td>0.5 (±1.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Brush</td>
<td>4.5 (±1.9)</td>
<td>1.0 (±1.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pinprick</td>
<td>5.0 (±2.1)</td>
<td>1.1 (±2.2)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Scores were assessed on a scale from 0 to 10, where 0 is "normal sensation" tested against a contralateral, nonpainful area, lower scores represent hypoesthesia (0 = no sensation), and higher scores represent hyperesthesia (10 = most intense/painful sensation).

* Data were not normally distributed (Shapiro–Wilk test), therefore analyzed by the Wilcoxon signed rank test, and presented as median (interquartile range).
Discussion

- Pain may not be entirely generated and perceived in the CNS.
- Rather, the afferent sensory input from the painful area plays a role in maintaining spontaneous pain in CPSP.
- It is plausible that the sensory neurons in the CNS, which are damaged by the stroke, become sensitized to the afferent stimuli, and generate action potentials secondary to trivial sensory input.
- Supporting the local afferent blockade (rather than the systemic effect) as the cause of pain relief is the finding that no changes in pain intensity occurred after the block in the ipsilateral painful extremity in these patients.
Conclusion

- CPSP has a variable time to onset after stroke.
- In most cases of CPSP, the stroke lesions are extrathalamic.
- Amitriptyline is the first-line drug of choice.
- If amitriptyline fails or is unavailable, then try lamotrigine.
- In intractable cases, short-term pain relief may be achieved by IV lidocaine, propofol, or ketamine.
- Motor cortex stimulation, DBS, or, rTMS may be tried in resistant CPSP patients.
- Sensory afferent input may play an important role in maintaining pain in CPSP.