Central Pain Syndrome

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Objectives

1. Differentiate causes of pain post acquired brain injury to appropriately diagnose true central pain syndrome
2. Critically review and analyze pain nomenclature, physiology and patho-etiologypatho-etiolo in the context of central pain
3. Examine the current literature to formulate a rational management protocol for central pain syndrome post acquired brain injury
Introduction to Pain

• Nomenclature
  – Acute pain vs chronic pain
  – Nociceptive / Neuropathic / Central

• Mechanisms based research
  – Peripheral and Central

• Evolving knowledge -> new definitions
Pain nomenclature

Neuropathic pain

• “Caused by a **primary** lesion or **dysfunction** in the **nervous** system” (Bogduk 1994)

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**Neurology**

Neuropathic pain: Redefinition and a grading system for clinical and research purposes
Neurology 2008;70:1630-1635 Published Online before print November 14, 2007
DOI: 10.1212/01.WNL.0000304434.08077.5d

**PAIN**

A new definition of neuropathic pain
Table: Grading system for neuropathic pain

Criteria to be evaluated for each patient

1. Pain with a distinct neuroanatomically plausible distribution
2. A history suggestive of a lesion affecting the peripheral nervous system
3. Demonstration of the distinct neuroanatomically plausible distribution by examination
4. Demonstration of the relevant lesion or disease by at least one confirmatory test

Flowchart:
- Loading complaint
  - Pain
    - Pain distribution neuroanatomically plausible and history suggests relevant lesion or disease
      - Yes
        - Working hypothesis: Possible neuropathic pain
          - Confirmatory tests:
            a: Negative or positive sensory signs, confined to innervation territory of the lesioned nervous structure
            b: Diagnostic test confirming lesion or disease explaining neuropathic pain
              - Both
                - Definite neuropathic pain
              - One
                - Probable neuropathic pain
        - No
          - Unlikely to be neuropathic pain
      - No
        - Unconfirmed as neuropathic pain

Mechanisms: Pain physiology

- Cortex
- Thalamus
- Midbrain projection to PAG
- Brainstem reticular formation
- Spinothalamic tract
- Dorsal horn of spinal cord
- Cell body in DRG
- Aδ and C fibres
- Spinoreticular tract
Labeled line to Gate control theory

Diagram:
- C fibre
- Aβ fibre
- Inhibitory interneurone
- Brain
Mechanisms: Pain physiology

- **Aδ and C fibres**
- **Cortex**
- **Thalamus**
- **Midbrain projection to PAG**
- **Brainstem reticular formation**
- **Spinothalamic tract**
- **Dorsal horn of spinal cord**
- **Cell body in DRG**

![Image of pain physiology mechanisms](image)

- **Aβ myelinated fibers**
- **Peptidergic C fibers**
- **Nonpeptidergic C fibers**

![Image of thalamic level](image)

- **Medial nuclear group**
- **Ventral nuclear group**
- **Anterior nucleus group**
- **Lateral nuclear group**
- **Internal medullary lamina**

![Image of pain pathways](image)

- **NS**
- **WDR**
AFFECTIVE COMPONENT

- Pain matrix

Pain imaging in health and disease Schweinhardt *J Clin Invest.* 2010;120(11):3788–3797
Defining Pain: Change in paradigm

- PAIN IS NOT SIMPLY A REFLECTION OF PERIPHERAL INPUTS OR PATHOLOGY BUT A DYNAMIC REFLECTION OF CENTRAL NEURONAL PLASTICITY

  - In a healthy state, this modulation is reversible so that pain is temporary and subsides with recovery

LATREMOLIERE WOOLF J PAIN 2009 10 895-926
PERSISTENT PAIN

• ACTIVITY-DEPENDENT PLASTICITY

• Structural, functional and biochemical changes in the PNS & CNS
  – Neurogenic inflammation
  – Central Sensitization
  – Autonomic dysfunction (sympathetic pain)
  – Hypothalamo-pituitary dysfunction

Woolf Pain 152 (2011) S2–S15
Peripheral Sensitization

- Neurogenic inflammation
Central Sensitization

Woolf Pain 152 (2011) S2–S15
Central Sensitization

Latremolier J Pain, Vol 10, No 9 (September), 2009: pp 895-926
CNS Changes with persistent pain

• **FUNCTIONAL & BIOCHEMICAL**

• **STRUCTURAL CHANGES**

  – *Change in spatial representation in the Pain Matrix*

  – *Grey matter decreased in insula, anterior cingulate cortex (ACC) and pre-frontal cortex (PFC)*

Pain imaging in health and disease Schweinhardt *J Clin Invest.* 2010;120(11):3788–3797
Central Sensitization Syndromes

- Plastic changes in CSS similar to changes in conditions with persistent pain
- Location not as relevant
- Genetics, Psyche factors

HOW DO WE CLINICALLY FIND CS?

• PRIMARY HYPERALGESIA -> PERIPHERAL SENSITIZATION
  – At site of injury
  – Thermal and mechanical

• SECONDARY HYPERALGESIA -> CENTRAL SENSITIZATION
  – Outside zone of injury
  – Mechanical stimuli only
  – e.g. arthritic knee

BJF DEAN Shoulder pain BJSM 2013
Different Painful Conditions can cause Central Changes

- **Acute**
  - Peripheral, nociceptive (OA, fracture, sprain)
  - Neuropathic (peripheral or central)
  - Central changes are reversible

- **Central sensitization syndromes**: pain and abnormal plastic changes

- **Chronic or Persistent Pain** irrespective of cause
  - Mechanisms / changes similar in Central Sensitization Syndromes and persistent pain
PAIN AFTER ACQUIRED BRAIN INJURY (ABI) - Central Pain Syndrome
ALL PAIN POST-ABI IS NOT CENTRAL PAIN

• Pain post ABI is multi-factorial
• Chronic pain: common in the elderly
• CPSP= Central Post-stroke pain
• PSP= Post-stroke pain

CPSP: Clinical characteristics, pathophysiology and Mx Klit Lancet Neurol 2009; 8:857-868
Mechanism based approach

Roosink Post-stroke shoulder pain: NeuroRehabilitation 30 (2012) 153–165
Central Pain POST-ABI

• NO PATHOGNOMONIC FEATURES
• Diagnosis of exclusion
  – May fulfil criteria for definite neuropathic pain despite pain being of nociceptive origin
  – Several different pain types often co-exist and if chronic-> CENTRAL SENSITIZATION
• Now thought of as a CENTRAL NEUROPATHIC PAIN DISORDER ONLY AFTER OTHER CAUSES ARE EXCLUDED
Central Neuropathic Pain

Common Causes

- CVA / TBI
- MS / PD
- Syrinx
- SCI
- AVMs
- Infections
CURRENT THINKING: CPSP vs PSP

- **CPSP**: a *central neuropathic pain syndrome* associated with *somatosensory abnormalities* due to *CNS lesion* following a vascular insult

- **PSP**: a broader range of clinical conditions leading to *pain after stroke*, but not restricted to pain of *central neuropathic nature*

DeOliviera et al: BMC Neurol 2012 Sep 11;12:89
### Panel 3: Diagnostic criteria for CPSP

#### Mandatory criteria for the diagnosis of CPSP
- 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 dysaesthesia to touch or cold

CPSP = central post-stroke pain.
Panel 4: Grading system for CPSP

Criteria to be evaluated for each patient (based on a grading system for neuropathic pain by Treede and co-workers).\textsuperscript{31} CPSP is defined as “possible” if criteria 1, 2, and 3 are fulfilled, “probable” if criteria 1, 2, and 3 plus either criteria 4 or 5 are fulfilled, and “definite” if criteria 1–5 are fulfilled.

1. Exclusion of other likely causes of pain
   No other obvious cause of pain

2. Pain with a distinct neuroanatomically plausible distribution
   Either pain localised unilaterally in the body and/or face or unilaterally on one side of the body with contralateral involvement of the face

3. A history suggestive of stroke
   Sudden onset of neurological symptoms with onset of pain at or after stroke onset

4. Indication of the distinct neuroanatomically plausible distribution by clinical neurological examination
   Findings of positive or negative sensory signs in the painful area on clinical examination, pain localised within a territory of sensory abnormality, and anatomically plausible distribution of sensory abnormalities

5. Indication of the relevant vascular lesion by imaging
   Visualisation of a lesion that can explain the distribution of sensory findings (either CT or MRI)

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Table: Grading system for neuropathic pain

<table>
<thead>
<tr>
<th>Criteria to be evaluated for each patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pain with a distinct neuroanatomically plausible distribution*</td>
</tr>
<tr>
<td>2. A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system*</td>
</tr>
<tr>
<td>3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test*</td>
</tr>
<tr>
<td>4. Demonstration of the relevant lesion or disease by at least one confirmatory test*</td>
</tr>
</tbody>
</table>

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Diagram: Grading system for neuropathic pain

[Flowchart showing the grading system for neuropathic pain]
POST-STROKE PAIN: EPIDEMIOLOGY

• Incidence: 8-55 %
  – Hansen 2012: > 45 % new pain, 10% CPSP
  – O’Donnell 2013*: 10.6%
  – Hansson 2004: Higher if somato-sensory abnormalities are present
  – Andersen 1995: most are extra-thalamic

• Presence of CPSP
  – Greater dependence + Cognitive decline
When do we see this?

- Slowly progressing patients represent a diagnostic challenge.
Pain symptoms in CPSP

Clinical features specific to CPSP

- One common feature in all CPSP patients is a disturbance of non-nocuous and/or nocuous temperature sensibility
- Only about half have abnormalities of touch and vibration
- Often outside zone of injury


Pain after TBI

• Nampiaparampil et al (JAMA 2008)
  – 23 studies (n=4206)
  – Mild TBI 75 %; mod-severe TBI 32%
  – Overall prevalence of chronic pain 51%
• Ofek et al (2007): Central pain following TBI
  – briefly mentioned in three case report studies
  – manifested in body regions not associated with injury
  – often delayed in onset
  – penetrating injuries often not different in presentation when compared to blunt injuries
**Pain after TBI**

*J Head Trauma Rehabil*  
Vol. 19, No. 1, pp. 72-81

### Table 2. Pathoetiologies of pain after traumatic brain injury

<table>
<thead>
<tr>
<th>Clinical classifications</th>
<th>Clinical entities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary musculoskeletal</td>
<td>Fracture, abrasion, laceration, sprain, strain, arthropathy, hematoma, contusion</td>
</tr>
<tr>
<td>Secondary musculoskeletal</td>
<td>Pressure ulcer, heterotopic ossification, reflex sympathetic dystrophy, adhesive capsulitis, tendonitis, myofascial dysfunction, tension headache</td>
</tr>
<tr>
<td>Vascular</td>
<td>Thromboembolism, arterial insufficiency, compartment syndrome, and migraine headache</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Radiculopathy, plexopathy, peripheral nerve lesion, complex regional pain syndrome, central pain, elevated intracranial pressure</td>
</tr>
<tr>
<td>Visceral</td>
<td>Cardiac, gastrointestinal, pulmonary, hepatic, renal, genitourinary</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Indwelling catheters and tubes, surgical incisions, etc</td>
</tr>
</tbody>
</table>
Central pain syndrome: MECHANISMS

- Spino-thalamic tract dysfunction
- Disinhibition
- Thalamic changes
- Central Sensitization
  - May be induced directly by ongoing nociception or by the brain lesion directly or indirectly by factors that are pre-morbid or related to the stroke
  - May initiate, maintain or worsen pain
Mechanisms are important
The role of screening tools in diagnosing neuropathic pain

Table 2. Main psychometric properties of neuropathic pain screening tools.

<table>
<thead>
<tr>
<th>Screening tool</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LANSS</td>
<td>85</td>
<td>80</td>
<td>86</td>
<td>84</td>
<td>[20]</td>
</tr>
<tr>
<td>S-LANSS</td>
<td>74</td>
<td>76</td>
<td>76</td>
<td>75</td>
<td>[25]</td>
</tr>
<tr>
<td>painDETECT</td>
<td>85</td>
<td>80</td>
<td>83</td>
<td>–</td>
<td>[13]</td>
</tr>
<tr>
<td>DN4</td>
<td>83</td>
<td>90</td>
<td>86</td>
<td>–</td>
<td>[21]</td>
</tr>
<tr>
<td>NPQ</td>
<td>67</td>
<td>74</td>
<td>71</td>
<td>–</td>
<td>[22]</td>
</tr>
<tr>
<td>ID pain</td>
<td>80</td>
<td>44</td>
<td>42</td>
<td>81</td>
<td>[42]</td>
</tr>
</tbody>
</table>

---: Not reported.

1Psychometric values presented for paper and pencil version of painDETECT.
2Psychometric values for ID pain have been calculated by hand as they are not reported in the original publication. To allow for comparison with the other screening tools, data from the original publication for nociceptive and mixed pain patients were collapsed and psychometric values were calculated based on neuropathic and non-neuropathic groups.

Treatment of Central Pain

• Rehab therapies
• Pharmacotherapy
• Non-pharmacotherapy
  – Magnetic stimulation (rTMS)
  – DBS & Invasive motor cortex stimulation
• Stellate ganglion blocks
• DREZ
• Spinal cord stimulation
Rehab therapies

• Desensitization
• Mirror therapy
• Modalities, including TENS
• Cochrane 2013 (Interventions for treating pain and disability in adults with CRPS)
  – Critical lack of high quality evidence
  – Low quality evidence of small positive effects that are not sustained
Table 3. Drugs Studied in Central Poststroke Pain and Their Mechanism of Action

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants Amitriptyline</td>
<td>Balanced monoamine reuptake inhibition</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Voltage-gated sodium-channel blockade</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Voltage-gated sodium-channel blockade</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Presynaptic voltage-gated sodium-channel inhibition thus reduced release of presynaptic transmitters</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Voltage-gated sodium-channel block and inhibition of glutamate release by an action on AMPA/kainase receptors</td>
</tr>
<tr>
<td>Gabapentine</td>
<td>Binding to α2δ subunit of presynaptic voltage-dependent calcium channels with reduced release of presynaptic transmitters</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Voltage-gated sodium-channel block</td>
</tr>
<tr>
<td>Anesthetics</td>
<td></td>
</tr>
<tr>
<td>Lidocain</td>
<td>Blockade of sodium channels thus preventing ectopic discharges</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Same as lidocain</td>
</tr>
<tr>
<td>NMDA receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>NMDA receptor antagonist</td>
</tr>
<tr>
<td>Analgesics</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>μ opioid-receptor agonist and monoamine reuptake inhibitor</td>
</tr>
<tr>
<td>Morphine</td>
<td></td>
</tr>
</tbody>
</table>
Pharmacotherapy

• Upto 2009: total of 6 RCTs (n=96)

• Multiple systematic reviews (> 10) of data involving the same RCTs
Review and recommendations

Pharmacologic management of neuropathic pain: Evidence-based recommendations

Table 1
Stepwise pharmacologic management of neuropathic pain (NP)

<table>
<thead>
<tr>
<th>Step 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess pain and establish the diagnosis of NP [25,20] if uncertain about the diagnosis, refer to a pain specialist or neurologist</td>
</tr>
<tr>
<td>Establish and treat the cause of NP; if uncertain about availability of treatments addressing NP etiology, refer to appropriate specialist</td>
</tr>
<tr>
<td>Identify relevant comorbidities (e.g., cardiac, renal, or hepatic disease, depression, gait instability) that might be relieved or exacerbated by NP treatment, or that might require dosage adjustment or additional monitoring of therapy</td>
</tr>
<tr>
<td>Explain the diagnosis and treatment plan to the patient, and establish realistic expectations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiate therapy of the disease causing NP, if applicable</td>
</tr>
<tr>
<td>Initiate symptom treatment with one or more of the following:</td>
</tr>
<tr>
<td>- A secondary amine TCA (nortriptyline, desipramine) or an SSNRI ( duloxetine, venlafaxine)</td>
</tr>
<tr>
<td>- A calcium channel α2-δ ligand, either gabapentin or pregabalin</td>
</tr>
<tr>
<td>- For patients with localized peripheral NP: topical lidocaine used alone or in combination with one of the other first-line therapies</td>
</tr>
<tr>
<td>- For patients with acute neuropathic pain, neuropathic cancer pain, or episodic exacerbations of severe pain, and when prompt pain relief during titration of a first-line medication to an efficacious dosage is required, opioid analgesics or tramadol may be used alone or in combination with one of the first-line therapies</td>
</tr>
<tr>
<td>Evaluate patient for non-pharmacologic treatments, and initiate if appropriate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reassess pain and health-related quality of life frequently</td>
</tr>
<tr>
<td>If substantial pain relief (e.g., average pain reduced to ≤3/10) and tolerable side effects, continue treatment</td>
</tr>
<tr>
<td>If partial pain relief (e.g., average pain remains ≥4/10) after an adequate trial (see Table 3), add one of the other first-line medications</td>
</tr>
<tr>
<td>If no or inadequate pain relief (e.g., &lt; 30% reduction) at target dosage after an adequate trial (see Table 3), switch to an alternative first-line medication</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>If trials of first-line medications alone and in combination fail, consider second- and third-line medications or referral to a pain specialist or multidisciplinary pain center</td>
</tr>
</tbody>
</table>

TCA, tricyclic antidepressant; SSNRI, selective serotonin and norepinephrine reuptake inhibitor.
Pharmacotherapy

- Amitryptiline: effective and well tolerated (II-B)
- Lamotrigine: moderately effective and well-tolerated (I-B)
- Fluvoxamine: effective (II-B)
- Carbamazepine: minimally effective (II-B)
- Gabapentin: not effective (III)
- Phenytoin / Topamax: inconclusive
- Morphine: ineffective (II-B)
- IV Lidocaine: short period (II-B)
Pharmacotherapy

- 1st line: Amitryptiline
- 1st / 2nd line: Lamotrigine
- 2nd line: Fluvoxamine
- Short term relief: IV Lidocaine / Propofol

Pregabalin in CPSP

• Randomized, double-blind, multicenter, placebo-controlled study of 150 to 600 mg/day pregabalin over 3 mth

• N=219

• Pain reductions at endpoint did not differ significantly

• Improvements in sleep, anxiety, and CGIC

Kim et al: Pain. 2011 May;152(5):1018-23
Keppra in CPSP

- double-blind, placebo-controlled, study design
- N=33
- No improvement of pain, GIC, sleep quality, QOL or depression

Treating CS

- Eliminate peripheral nociceptive input
- Pharmacotherapy
  - SSRIs, SNRIs, topicals
  - opioids
  - NMDA antagonists, CA channel antagonists
  - Education
- Exercise therapy
- CBT

Tx of CS in unexplained chronic pain Nijs Exp Opin Pharmacother 2014
Non-pharmacologic therapy

- rTMS
  - Safe and effective in CPSP (II-A)
- Considered in drug-resistant patients only
  - Motor cortex stimulation
  - Invasive motor cortex stimulation
  - DBS
- Not adequate experience with DREZ, SCS
SGB in CPSP

- Yoo 2012: n=42 US guided SGB vs blind in post-stroke CRPS

**Table 2. Changes of Visual Analogue Scale**

<table>
<thead>
<tr>
<th></th>
<th>Before injection</th>
<th>2 weeks after injection</th>
<th>4 weeks after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind group</td>
<td>5.09±1.13</td>
<td>3.21±1.44</td>
<td>2.12±1.06*</td>
</tr>
<tr>
<td>US-guided group</td>
<td>5.24±1.61</td>
<td>2.63±1.64*</td>
<td>1.38±0.98*</td>
</tr>
</tbody>
</table>

**Table 3. Intergroup Comparison of the Efficacy by Stellate Ganglion Block**

<table>
<thead>
<tr>
<th></th>
<th>2 weeks after injection</th>
<th>4 weeks after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blind group</td>
<td>US-guided group</td>
</tr>
<tr>
<td>Δ VAS</td>
<td>1.88±0.62</td>
<td>2.61±1.09*</td>
</tr>
<tr>
<td>Δ Volume of Hand (ml)</td>
<td>61.21±36.43</td>
<td>67.38±27.73</td>
</tr>
<tr>
<td>Δ Score of CSC</td>
<td>1.91±1.40</td>
<td>2.33±1.22</td>
</tr>
</tbody>
</table>
Evidence based practice

Ethical practice