Mystery of Central Post stroke Pain
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Central pain:

- Definition and causes
- CPSP and other types of post stroke pain
- Mechanisms
- Management of central pain
Pain: From static to dynamic

Modified from Casey 2006
Tracey & Mantyh, 2007
Central Pain: Pain arising as direct consequence of a lesion or disease affecting the somato-sensory system (Neurology 2008).
Central Post Stroke Pain:
Thalamic syndrome

- Slight hemiplegia
- Sensory disturbance
- Hemiatxia, hemiastereognosis
- Intolerable pain
- Choreo-athetoid movements

Dejerine and Roussy 1906
## Central pain: Characteristics and causes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system lesion</td>
<td><strong>Spinal</strong></td>
</tr>
<tr>
<td>Spontaneous and evoked pains</td>
<td><strong>Stroke</strong></td>
</tr>
<tr>
<td>Deep and superficial pain</td>
<td>Spinal cord injury</td>
</tr>
<tr>
<td>Paradox sensation: loss and hyperalgesia</td>
<td>myelitis</td>
</tr>
<tr>
<td>Thermal loss obligatory</td>
<td>syringomyelia</td>
</tr>
<tr>
<td>Thermal hyperalgesia</td>
<td>MS</td>
</tr>
<tr>
<td></td>
<td>cordotomy</td>
</tr>
<tr>
<td></td>
<td>DREZ</td>
</tr>
<tr>
<td></td>
<td><strong>Brain</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Stroke</strong></td>
</tr>
<tr>
<td></td>
<td>brain injury</td>
</tr>
<tr>
<td></td>
<td>MS</td>
</tr>
<tr>
<td></td>
<td>epilepsy</td>
</tr>
<tr>
<td></td>
<td>syringobulbia</td>
</tr>
<tr>
<td></td>
<td>Parkinson disease ?</td>
</tr>
</tbody>
</table>
Post stroke pain: case

48 yr, F. Sudden left hemiparesis
Gaze palsy, L hemiparesis
L. sensory loss
DWI lesion in the R. hemisphere
Thrombolysis
Day 2 large MCI infarction

CTC Day 1
CTC Day 2

Acute MR – DWI
Post Stroke Pain: Case

2007: Day 3 after stroke pricking sticking sensation L side
Cold allodynia L side

2010: 3 yrs after stroke
Constant pain L. face, arm, trunc
Deep burning, pricking pain
VAS pain intensity 8
Central pain:

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<table>
<thead>
<tr>
<th>Study</th>
<th>N with stroke</th>
<th>Total with Pain</th>
<th>Follow-up (Months)</th>
<th>N with CPSP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen et al. 1995</td>
<td>207</td>
<td>-</td>
<td>12</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>MacGowan et al. 1997</td>
<td>63 with LMI</td>
<td>-</td>
<td>60</td>
<td>16 (25%)</td>
</tr>
<tr>
<td>Bowsher et al. 2001</td>
<td>72 (Q to 1071 pts)</td>
<td>-</td>
<td></td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Weimar et al. 2002</td>
<td>119</td>
<td>-</td>
<td>12</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>Widar et al. 2002</td>
<td>616 (356 included)</td>
<td>43</td>
<td>24</td>
<td>15 (4%)</td>
</tr>
<tr>
<td>Glader et al. 2001</td>
<td>3203</td>
<td>20%</td>
<td>24</td>
<td>Not specified</td>
</tr>
<tr>
<td>Kong et al. 2004</td>
<td>107</td>
<td>45</td>
<td>19.8</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Jönsson et al. 2006*</td>
<td>297</td>
<td>62</td>
<td>16</td>
<td>4 (1%)*</td>
</tr>
</tbody>
</table>

* If the investigator suspected CPSP the patient was referred to a neurologist who diagnosed CPSP according to established criteria.
Post stroke Pain Case

2004
- 65 yr F Acute L hemiparalysis
- CT: Haemorrhage R thalamus
- Within months severe pain L. side

2008
- Spastic L. hemiparesis.
- Sensory disturbance L. side
Post Stroke Pain case

1. Shoulder pain
2. Sharp cutting pain L arm and hand (NRS:6) and leg (NRS:9). Cold allodynia
3. Painful spasms and spasticity L. leg
Post stroke pain

**Central Pain** = Pain caused by lesion or disease in the central nervous system (IASP, 1994)

**Problems:**
No precise criteria for delineating other pain conditions from CPSP

Klit et al. 2009 Lancet Neurology
CPSP: Delineation

Stroke unrelated pain

Stroke

Pain
CPSP: Delineation

Stroke related pain:
Musculoskeletal pain
Spasticity
Headache
Central Pain
CPSP: Delineation

Stroke related pain:
Musculoskeletal pain
Central Pain
CPSP: Delineation

Stroke related Pain
Central pain

The epidemiology and characteristics of post stroke pain incl. CPSP is addressed in two ongoing studies:
Retrospective
Prospective

Criteria for CPSP will affect the incidence of CPSP
Criteria for CPSP

1. Development of pain after stroke onset

1A Development of pain after onset of stroke, not attributed to headache, shoulder pain or joint pain

2. Overlap between areas of altered sensation and pain

3. Plausible distribution of area of pain or altered sensation (unilateral or crossed)

4. No other obvious source of pain

Klit et al. 2009 Lancet Neurol
Central pain:

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Stroke Pain: Distribution of Pain and sensory abnormality corresponds to brain territory destroyed by lesion

Vestergaard et al. 1995.
75 yr old M: Crossed central pain syndrome

Age 68: shortlasting vertigo
- Age 72: L. brainstem infarction
- L. facial and R. hemibody pain
- Burning Pain evoked by touch
75 yr old M: L brainstem stroke
Crossed pain syndrome

Pain

Sensation

Temperature (°C)

Left Face

Right Face

Left arm

Right arm
Distribution of Pain in Post Stroke Pain
Post Stroke: Central Pain and Sensory Abnormality

Neuropathic pain: Pain distribution represents a fraction of the deafferented area.

Combination of deafferentation and clinical hypersensitivity suggest hyperexcitability in neurons that have lost their normal input.
Central Post Stroke Pain: Touch allodynia

<table>
<thead>
<tr>
<th>Touch</th>
<th>No Pain N=71</th>
<th>Pain N=16</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5(7%)</td>
<td>2(3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased</td>
<td>65(92%)</td>
<td>12(75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Increased</td>
<td>1(1%)</td>
<td>1(16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Allodynia</td>
<td>0</td>
<td>9(56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>0</td>
<td>8(50%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allodynia or dysesthesia</td>
<td>0</td>
<td>12(75%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Andersen et al. 1995
Central Post Stroke Pain:
Cold Allodynia

<table>
<thead>
<tr>
<th>Temp 20 ⁰C</th>
<th>No Pain N=71</th>
<th>Pain N=16</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>28(39%)</td>
<td>1(6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Decreased</td>
<td>37(52%)</td>
<td>8(50%)</td>
<td>NS</td>
</tr>
<tr>
<td>Increased</td>
<td>6(8%)</td>
<td>7(44%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allodynia</td>
<td>0</td>
<td>9(56%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>2(3%)</td>
<td>12(75%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allodynia or</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>Dysesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Central post stroke Pain: Mechanisms

- Pain within area of sensory abnormality
- Pain area: Fraction of sensory loss
- Sensory loss and hypersensitivity.
- Loss of input to thalamus → Pain in corresponding body territory
Central pain: Mechanisms

A. Lat Thal → Med Thal

Loss of input disinhibition medial thalamus (Head and Holmes 1911)

B. Insula → ACC → Med Thal

Loss of cold input to insula disinhibition medial thalamus (Craig et al., 2000)

C. Thal

Loss of ascending input to thalamus
Bursting activity by low Ca spikes (Wang & Thompson 2008).

D. Thal

Lesion
Central pain:

- Definition and causes
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- Mechanisms
- Management of central pain
Management of central pain
– reduce sensitization

Treatment Principles
• Reduce peripheral sensitisation
• Reduce activity in DRG
• Reduce ectopic activity
• Decrease central sensitisation
• Reduce central facilitation
• Increase central inhibition

Pharmacological treatment
Stimulation therapy
• TNS
• Deep brain stimulation
• Motor cortex stimulation

Psychological / other treatments
• Cognitive behavioural therapy
• Hypnosis etc
• Physiotherapy
• Educational programmes
• Other
Neuropathic Pain: Pharmacology

- **Antidepressants**
  - Tricyclic antidepressants
  - SSRI
  - SNRI
- **Anticonvulsants**
  - Gabapentin
  - Pregabalin
  - Valproic acid
  - Topiramate
  - Carbamazepine
  - Oxcarbazepine
  - Phenytoine
  - Lamotrigine
- **Opioids**
  - Morphine
  - Oxycodone
  - Tramadol
- **NMDA antagonists**
  - Memantine
  - Amantadine
  - Dextromethorphan
- **Cannabinoids**
- **Topicals**
  - Lidocaine
  - Capsaicin
- **Other**
  - Levetiracetam
  - Botulinum toxin
# Central Pain Management:
## Mechanisms of drugs

<table>
<thead>
<tr>
<th>Pharmacological Agents</th>
<th>Mechanism/Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Non-specific sodium channel blockade</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>Non-specific sodium channel blockade</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Non-specific sodium channel blockade</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Specific sodium channel blockade</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Binding to $\alpha_2\delta$-subunit calcium channel</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Binding to $\alpha_2\delta$-subunit calcium channel</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>GABAergic, sodium channel blockade</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>NMDA-antagonist</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>NA and 5-HT reuptake inhib., NMDA-antagonist, Na block</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>NA and 5-HT reuptake inhibitor</td>
</tr>
<tr>
<td>Morphine</td>
<td>$\mu$-opioid receptor agonist</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Cannabinoid receptor interaction</td>
</tr>
</tbody>
</table>
# Central Post stroke Pain: Controlled clinical trials

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Drug Dose</th>
<th>Study</th>
<th>Design N</th>
<th>Result</th>
<th>NNT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ Channel blocker</td>
<td>CBZ 800 mg</td>
<td>Leijon and Boivie 1989</td>
<td>Cross-over 15</td>
<td>Cbz= pla</td>
<td>3.4 (2-105)</td>
</tr>
<tr>
<td>5-HT and NA reuptake inhibitor</td>
<td>Amitriptyline 75</td>
<td>Leijon and Boivie 1989</td>
<td>Cross-over 15</td>
<td>Ami&gt; Pl</td>
<td>1.7 (1-3)</td>
</tr>
<tr>
<td>Na⁺ Channel Blocker glutamate</td>
<td>Lamotrigine  &gt; 200 mg</td>
<td>Vestergaard et al. 2001</td>
<td>Cross- over 30</td>
<td>Ltg&gt;pla</td>
<td>NA</td>
</tr>
<tr>
<td>binding Ca²⁺ channel</td>
<td>Pregabalin 300-600 mg</td>
<td>Vranken et al. 2007</td>
<td>Parallel 19</td>
<td>Preg &gt; Pl</td>
<td>3.3 (2-15)</td>
</tr>
</tbody>
</table>
Central Post stroke Pain: Evidence recommendation

**Receomdation:**
Level A: Pregabalin (SCI) Cannabinoid (MS)
Level B: Lamotrigine, Gabapentin
Level B no effect: Valproate and mexilitine (SCI)
Level C: Opioids

Finnerup et al. 2005
Attal et al. 2006, 2010
1966-April 2005: 18th Jan 2010: Increase:
105 RCTs 168 RCTs 60%
59 (56%) cross-over 79 (47%) cross-over 34%
46 (44%) parallel 89 (53%) parallel 93%
Neuropathic pain

Peripheral
- TCA
- \(\alpha\)-2-\(\delta\) agent
- SNRI
- Tramadol, Topical capsaicin, Lidocaine patch, opioids, combination therapy

Central
- TCA
- \(\alpha\)-2-\(\delta\) agent
- opioids, Lamotrigine, cannabinoids combination therapy

Cause
Comorbidity
Contraindica.
Cost
Conclusion: Post stroke Pain

- Post stroke pain different types of pain
- Central pain not uncommon.
- Clinical signs of neuronal hyperexitability
- Pathophysiology hypothetical
- Pharmacological modulation with anti-hyperexcitable compounds may be useful
Thanks to all collaborators at DPRC:
Opening speech from IASP President
the 2nd ASEAPS congress Kuala Lumpur
IASP and South East Asia
What can IASP do?

Countries with IASP chapters
Countries without IASP chapters
IASP send its warm wishes to:

Hong Kong Pain Society

Troels S. Jensen

www.iasp-pain.org
See You in Montréal
August 2010

MONTRÉAL 2010 13th WORLD CONGRESS ON PAIN®
Aug 29 – Sept 2  www.iasp-pain.org/Montreal
Thanks to all collaborators at DPRC: