Assessment of Neuropathic Pain
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Peripheral Neuropathic Pain case

- 42 yr. old F
- Tibial fracture 1996
- 1996 removal of ostesynthesis
- 1998 removal of neuroma peronal nerve
- Constant burning pain in malleol area
- Evoked pain in lower leg and foot
- VAS pain: 5-10

Characteristics

- Sensory loss
- Spont + evoked pain
- Allodynia/hyperalgesia
- Specific sensory pattern
- Paroxysms
- Aftersensations
- Abnormal summation
Neuropathic Pain = Pain initiated or caused by a primary lesion, dysfunction or transitory perturbation of the peripheral or central nervous system (IASP, 1994)

Neuropathic Pain = Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system (Treede et al. Neurology 2008).

**Neuropathic Pain: Definitions**

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spontaneous symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>– Spontaneous pain</td>
<td>Persistent burning, intermittent shock-like or lancinating pain</td>
</tr>
<tr>
<td>– Dysesthesias</td>
<td>Abnormal unpleasant sensations e.g. shooting, lancinating, burning</td>
</tr>
<tr>
<td>– Paraesthesias</td>
<td>Abnormal, not unpleasant sensations e.g. tingling</td>
</tr>
<tr>
<td><strong>Evoked symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>-- Par/dysesthesia</td>
<td>Abnormal, (un)pleasant sensations e.g. tingling</td>
</tr>
<tr>
<td>– Allodynia</td>
<td>Painful response to a non-painful stimulus e.g. warmth, cold, pressure, stroking</td>
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<tr>
<td>– Hyperalgesia</td>
<td>Increased response to a painful stimulus e.g. pinprick, cold, heat</td>
</tr>
<tr>
<td>– Hyperpathia</td>
<td>Delayed, explosive response to a painful stimulus</td>
</tr>
</tbody>
</table>
### Chronic Pain: Classification

<table>
<thead>
<tr>
<th>Neuropathic</th>
<th>Nociceptive</th>
<th>Mixed Pain</th>
<th>Idiopathic Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve injuries</td>
<td>Osteoarthritis</td>
<td>Cancer Pain</td>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Amputations</td>
<td>Rheum. arthritis</td>
<td>Neck pain</td>
<td>Bodyly distress</td>
</tr>
<tr>
<td>Plexus avulsion</td>
<td>Postop pain</td>
<td>Low Back pain</td>
<td>Whiplash injury</td>
</tr>
<tr>
<td>PHN</td>
<td>Colitis</td>
<td>Limb Pain</td>
<td>Irrit. bowel disease</td>
</tr>
<tr>
<td>Trig. neuralgia</td>
<td>Tendinitis</td>
<td>Visceral pain</td>
<td>Interstitial cystitis</td>
</tr>
<tr>
<td>Neuropathies</td>
<td>Myositis</td>
<td>Thoracic pain</td>
<td></td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>Migraine ?</td>
<td></td>
<td></td>
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<tr>
<td>MS</td>
<td>CRPS ?</td>
<td></td>
<td></td>
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<tr>
<td>Spinal cord injury</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CRPS ?</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other</td>
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</tbody>
</table>

Woolf 2004
Finnerup & Jensen 2005

### Chronic pain: Classification ("splitting")

- **Neuropathic Pain**
- **Inflammatory Pain**
- **Idiopathic pain**
**Chronic pain:** Classification ("lumping")

- **Neuropathic Pain**
- **Inflammatory Pain**
- **Mixed Pain**
- **Idiopathic pain**

**Peripheral Neuropathic pain:** Diagnostic methods

- History
- Neurological exam incl. Sensory exam.
- Neurography
- Quantitative sensory testing (QST)
- Challenging stimulus (capsaicin/heat/cold)
- Microneurography, EMG
- Imaging (X-Ray, CT, MRI, fMRI, PET EEG)
- Nerve/skin biopsies, surgical exploration
- Pharmacological trials
**Bedside tests:**
Thermal, touch, brush, pinprick, pressure, TP discrimination

**Record:**
Normal
reduced
increased

**Specific tests (QST):**
Thermo, brush area
pinprick area, algometry
Skin biopsies

**Quantitative sensory testing:**
Thermo-testing

Chronic Pain: Assessment of Pain

VAS

NRS

"Pain intensity"

Suffering

Pain

Nociception

Thermal-evoked
static-evoked
Pinprick-evoked
Brush-evoked

global ongoing evoked fatigue malaise depression
Small fibre neuropathy

- 77 yr., M
- Prior history of Pagets disease and coronary heart disease
- For 2 yrs. burning smarting pains in feet. Pain provoked by walking.
- Normal muscle function. Tendon reflexes all normal
- Reduced sensitivity to pinprick and cold form ankle and distally
- Normal sensitivity to touch, vibration and position

Summary:
Reduced pinprick threshold
Reduced thermal detect. threshold
NP Grading system: Criterion 1

1. **Pain with a distinct neuroanatomically plausible distribution.**

A region corresponding to a peripheral innervation territory or to the topographical representation of a body part within the CNS.

**Pain drawing**
Example: Distal sensory neuropathy

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**NP Grading system: Criterion 2**

2. **A history of a relevant lesion or disease affecting the peripheral or central somato-sensory system.**

The lesion or disease is reported to be associated with pain with a temporal relationship typical for the condition.

**Medical history**
Example:
- 43 yr. old Female
- IDDM for 20 years.
- For 5 years numbness in feet
- Last 4 years burning pain in feet
- Last 2 years tingling in fingertips.
NP Grading system: Criterion 3

3. Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test.

As part of the neurological examination, these tests confirm the presence of neurological signs concordant with the distribution of pain.

Confirmatory tests:

NP Grading system: Criterion 4

4. Demonstration of the relevant lesion or disease by at least one confirmatory test.

As part of the neurological examination, these tests confirm the diagnosis of the suspected lesion or disease. These confirmatory tests depend on which lesion or disease is causing neuropathic pain.

Confirmatory tests:
Small fibre Neuropathies: Biopsy

**Technique:**
3 mm punch skin biopsies
Sterile condition lidocaine anesthesia
Immunostaining of 50 μm sections

**Markers used:**
PGP 9.5 non-specific panaxonal marker
Antibodies against microtubules
Antibodies against neurofilaments
Antibodies against myelin
Immunostaining against TRPV1, VIP, CGRP, SP

Staining for PGP 9.5
A: Normal
B: Diabetic neuropathy


Neuropathic Pain: New grading proposal

Leading complaint

History
Pain distribution neuroanatomically plausible and history suggest relevant lesion or disease
No
Neurology - Unlikely to be neuropathic pain
Possible NP

Examination
Confirmation tests:
1. Negative or positive sensory signs, confined to innervation territory of lesioned nervous structure
2. Diagnostic test confirming lesion or disease explaining neuropathic pain
Neither
Unconfirmed as neuropathic pain

Definite NP
Probable NP

Painful Polyneuropathies

- **Metabolic**
  - Vitamin deficiency
  - Diabetic
  - Insulinoma
  - Malnutrition
- **Drugs**
  - Antiretrovirals
  - Antineoplastic
  - Nitrofurantoin
  - Thalidomide
  - Disulfiram
- **Toxins**
  - Alcohol
  - Acrylamide
  - Arsenic
  - Thallium
- **Hereditary**
  - Amyloid
  - Fabry
  - HSAN type I
  - Tangier
- **Malignant**
  - Dysglobulinemia
  - Direct infiltration
  - Paraneoplastic
- **Infectious/Postinfectious**
  - Vasculitis
  - Zoster
  - Lepra
  - HIV
  - Guillain-Barre
- **Others**
  - Erytromelalgia
  - Idiopathic small fibre neuropathy
  - Cold injury

Investigations in painful peripheral neuropathy

- **Blood**
  - Full Blood count
  - SR
  - Renal function
  - Liver function
  - Ca++
  - Glucose
  - Fasting lipids lipoproteins
  - B12 Auto antibodies
  - Anti neuronal antibodies
  - Cryoglobulins
  - HIV serology
- **Urine**
  - Urinalysis
  - Bence Jones protein
  - Porphyrines
- **CSF**
- **X-Ray of thorax**
- **Electrodiagnostics**
  - NCS/EMG
  - QST
  - (Sympathetic skin response)
  - Autonomic function
- **Histopathology**
  - Nerve biopsy
  - Muscle biopsy
  - Skin biopsy

Modified from Scadding 2006
Handbook of Neurology

Modified from Ginsberg 2006
Handbook of Clin Neurology
Diabetes and neuropathy: Prevalence

Diabetes
2000: 2.8%
2030: 4.4% (366 mil individuals)
(Wild et al. 2004)

Diabetes and Neuropathy
Male: 71% clinical neuropathy after 12 yrs
Female: 51% clinical neuropathy 12 yrs
(United Kingdom Prospective Diabetes Study, 1998)

Diabetic Neuropathy: Classification

Rapidly reversible DN
Hyperglycemic neuropathy

Generalized sym. polyneuropathy
Acute sensory
Chronic sensory-motor
Autonomic

Focal and multifocal neuropathy
Cranial
Isolated peripheral (limb)
Mononeuritis multiplex
Truncal (thoracolumbar)
Proximal motor (amyotrophy)

Superimposed CIDP

Chronic sensory-motor
• “Dying back” or “length-dependent” (LD) process
  – Longest nerves affected first
  – End of nerve fibres preferentially affected
  – Time course: months to years
  – Gradual, symmetric
  – Symptoms: predominantly sensory

Modified from PK Thomas 2003.
Painful Diabetic Neuropathy: Classification and symptoms

- **Painful Diabetic neuropathy**
- **Focal and multifocal**
  - Cranial e.g N. III mono NP
  - Focal limb NP e.g. entrapment NP
  - Amyotrophy (proximal motor)
  - Truncal radiculoneuropathy
- **Generalized symmetric PN**
  - Acute sensory (always painful)
  - Chronic sensorimotor

- **Symptoms and signs**
  - Paresthesia, Numbness, dysesthesia/allodynia in feet/hands
  - Paroxysmal, shooting pain
  - Deep aching pain, muscle pain, cramping
  - Alloodynia and hyperpathia
  - Autonomic dysfunctions (associated)

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Symptoms in PDN: Related to fibre types?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Large Fibre Neuropathy</th>
<th>Small Fibre Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbness, P&amp;N</td>
<td>Burning, electric shocks</td>
<td>Pain:</td>
</tr>
<tr>
<td>Tingling</td>
<td>Stabbing</td>
<td></td>
</tr>
<tr>
<td>Poor balance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflexes,</td>
<td>Thermal, pin-prick sensation</td>
<td></td>
</tr>
<tr>
<td>proprioception vibration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure, balance,</td>
<td>Pain sensation, protective</td>
<td></td>
</tr>
<tr>
<td>muscle strength</td>
<td>sensation</td>
<td></td>
</tr>
<tr>
<td>NCV testing</td>
<td>Historically “invisible”</td>
<td></td>
</tr>
<tr>
<td>Sural nerve biopsy</td>
<td>QST</td>
<td></td>
</tr>
<tr>
<td>Diagnostic Test</td>
<td>Nerve biopsy, skin biopsy</td>
<td></td>
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</table>
Small Fibre Neuropathy SFN

Complaints
- Deep aching pain
- Burning feet
- Pricking sticking sensations

Examination
- Reduced thermal and pain sensation
- Loss of vibration distally in toes but normal at ankles
- Standard nerve conduction studies normal

Delineation
- A subtype of sensory neuropathies predominantly affecting C and A\(\delta\) nerve fibres

Herpes zoster and PHN
**Complaints:**
I have pain
I wake up with cramps
I feel miserable.
I can’t use my hand
I can’t work,
My family has left me

**Pain case:**
Objective measures

- Peripheral

- Central

**Signs**
sensory loss
Hyperalgesia
Allodynia
Target mechanisms
Neuropathic pain:
Modulation of spontaneous
and evoked pain

**Management**
Antidepressants, NMDA antag., Anticonv.
Physical therapy
Social support
Psychological support

**Complaints:**
I have pain
I wake up with cramps
I feel miserable.
I can’t use my hand
I can’t work,
My family has left me
3rd pain case

- 52 yr old woman mastectomised 4 yrs. ago because of ductal carcinoma
- Glands removed from the axilla followed by radiotherapy
- Has had pain and sensory loss in the right arm since operation
- Complains of swelling of the right arm
- Within the last 6 months increasing pains in the arm and in the spine
- A discrete limping of the right leg has been noted

**Diagnosis?**
**Treatment?**

### Causes of Pain: Cancer

- **Cancer-related**
  - Bone
  - Nerve compression/ infiltration
  - Soft tissue infiltration
  - Visceral
  - Muscle spasm
  - Lymphoedema
  - Raised intracranial pressure
  - Spinal cord compression

- **Treatment related**
  - Surgery: postoperative scars/adhesions
  - Radiotherapy: burns/ fibrosis
  - Chemotherapy: neuropathy

- **Associated with cancer/ debility**
  - Constipation
  - Pressure sores
  - Bladder spasms
  - Stiff joints
  - Post-herpetic neuralgia

- **Unrelated to cancer**
  - Arthritis
  - Angina
  - Trauma
  - Prior pain conditions
Comorbidities and problems in chronic pain

- Biological factors
- Psychological factors
- Social factors

Symptoms and signs in chronic pain categories

<table>
<thead>
<tr>
<th>Pain</th>
<th>Neuropathic</th>
<th>Nociceptive</th>
<th>Mixed</th>
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<tbody>
<tr>
<td>Positive symptoms and signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signs of inflammation</td>
<td>no</td>
<td>sometimes</td>
<td>sometimes</td>
</tr>
<tr>
<td>Neuroanatomical distribution</td>
<td>yes</td>
<td>no</td>
<td>variable</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>cold allodynia</td>
<td>often</td>
<td>rarely</td>
<td>?</td>
</tr>
<tr>
<td>Hyperpathia</td>
<td>sometimes</td>
<td>never</td>
<td>sometimes</td>
</tr>
<tr>
<td>after sensations</td>
<td>often</td>
<td>Rarely</td>
<td>?</td>
</tr>
<tr>
<td>Specific</td>
<td>Paroxysms ?</td>
<td>throb pain ?</td>
<td>none</td>
</tr>
<tr>
<td>Negative symptoms and signs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red. sensation in painful area</td>
<td>often</td>
<td>no</td>
<td>sometimes</td>
</tr>
<tr>
<td>Sensory loss of neural area</td>
<td>yes</td>
<td>no</td>
<td>sometimes</td>
</tr>
<tr>
<td>Motor deficit</td>
<td>Often</td>
<td>no</td>
<td>sometimes</td>
</tr>
</tbody>
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