Patho-physiology of Nervous System
Talk 1 – Pain and Motor disorders

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How the brain works.
Talks on NS

Talk 1 - This - Pain and Motor disorders
Talk 2 - Syndromes in neurosciences
Talk 3 - Disorders of special senses
Talk 4 - Cognitive functions, dementias, etc.
Outline

- Pain
- Motor disorders
Pain
A. Peripheral Mechanisms of Pain

- Injury
- Pathogen
  - Blood clotting
  - Necrosis
  - Ischemia
  - Proteins

- Inflammation
  - Histamine
  - Bradykinin
  - Serotonin
  - $K^+$
  - $H^+$
  - PGE$_2$
  - Leukotrienes

- Sensitization
  - CGRP, SP

- Edema formation
  - Tissue pressure

- Vasodilation, vascular permeability

- Non-noxious stimuli
- Noxious stimuli

- Hyperalgesia
- Allodynia

CGRP (Calcitonin-gene related peptide), SP (Peptide substance)
Tissue injury leads to painful sensation

Pain:
1 is a warning that something goes wrong
2 helpful to diagnostics and localization pathologies
3 can be pathologic, annoying beyond the purpose

Psychological pain components

Algothymic component is its emotional context
Algognostic component says, where, what and how much gets wrong

Pains, which lose the warning purpose are …neuralgic pains
neurologic investigation shows no deviation from norm.

Psychophysics: - no relation between stimulus intensity and percept intensity
- there is continuous transition between various touch and pain sensations
tickling, sharp point touch, warm, cold vs.
itching, puncture, scalding (opaření), congelation
what itches, we scrub (scrape) (?), …[Fenistil – antihistaminic, antipruriginous drug]
Pain is modified by...

- previous experience, expectations
- instruction, suggestion
- emotions, especially fear and anxiety
- concurrent activation of other sensory inputs
- diversion/ redirection of attention
Pain leads to activation of...

- sympathetic n.s.
  vasoconstriction, hypertension, tachycardia, sweating, paleness, goose flesh, mydriasis
- parasympathetic n.s.
  hypotension, bradycardia, nausea/vomiting
- motor response
- conscious response
Types of pain, phenomenology

Patho-genetic classification of pain
• receptive (nociceptive)
• peripheral neurogenous (neuropathy)
• central neurogenous
• originating in autonomous nervous system (Sympathetic n.s.)
• visceral
• pain of psychical origin

**Acute pain**
- cause can be identified
- short term
- disappears when the original cause is cured
- usually does not recurr

**Chronic pain**
- longer than 6 months
- cause may not be identified
- intensity higher than expected to known stimulus
- causes high physical and psychical stress
- annoying in daily life
Nociceptors, pain receptors = dedicated receptors, ion channels and free nerve endings

- They are sensitive on the **pH changes** (pH in acute abscess, phlegmona reaches 5.8 = pain, pH in chronic abscess is normal, without pain)

- Nociceptors register the **ratio K⁺:Ca²⁺**
  (threshold for pain is lower in the lower Ca²⁺ level in ECV)

- Evoking inflammation are (permeability of vessel wall, oedema) histamin, bradykinin, serotonin

- Direct influence of free-nerve endings:
  potassium, histamin, bradykinin serotonin

- Sensitisation of nociceptors:
  prostaglandins, esp. PGE₂, interleukin-1, interleukin-6, cyclooxygenases (COX-1, COX-2)

- From activated free nerve endings P-substance is released.
  It influences vessel wall (vasodilation, permeability of vessel wall, oedema) and mast cells (release of histamin after degranulation).
Fibres conducting nociceptive stimuli

- **C-fibres** – without myelin sheets, action potentials are convected slowly, fibres convect deep, nonaccurate localized, diffuse pain.

- **Aδ-fibres** – with thin myelin sheet, fibres mediate fast conduction of sharp, accurate localized pain.

- **Aα/Aβ-fibres** – large myelinated. Fibres do not convect nociceptive stimuli, they mediate tactile stimuli.

- Afferent fibres enter dorsal spinal roots. In this region exist excitatory and inhibitory interneurons. Inhibitory interneurons gate the passage of information into thalamus and cortex.
Painful stimuli

- chemical

- endogenous inflammation mediators (bradykinin, prostaglandins, serotonin, histamin, K+, H+, Il-1)

- exogenous substances (capsaicin, formalin)

- low/high temperatures

- temperature above 42°C is damaging

- mechanical
During painful stimuli...

- are activated tetrodotoxin resistant (TTX-R) channels
- ATP is released from damaged cells and acts as pain mediator. ATP receptors are purin receptors (P₂X)
- vaniloid receptors (VR₁) are receptors for capsaicin, also activated above 42°C
- activated acid sensing ion channels (ASIC), when pH < 6.5
- Up-regulation of post-synaptic receptors of excitation neuro-transmitters - glutamate (NMDA) and substance P (NK₁)
Pain gating control – spinal cord

Substantia gelatinosa
II. and III. Rexed zone
Opioid system and others

- nigro-striatal and meso-limbic, dopaminergic
  - motor systems and reward pathways
- hypothalamo-hypophyseous
  - central hormone modulation
- ascendent and descendent pathways
  - modulation
  - ascendent – spinal cord, talamus
  - descendent – peri-aqueductal grey, nuclei raphe
Endogenous opioids

- β-endorphine (31 AA) - μ
- Endomorphine (4 AA) - μ
- Leu-enkefalin (5 AA) - δ
- Met-enkefalin (5 AA) - δ
- Dynorphine(A:AA 1-8, B:AA1-17) - κ
- nociceptin/ orphanin
- nocistatin
- pre-synaptic receptors
  - Inhibiting neuro-transmitter release
  - ↓ Ca²⁺
- post-synaptic receptors
  - ↑ K⁺ conductance – hyperpolarization

Endogenous cannabinoids

- amids and esters of fatty acids
- anandamid
- palmitoyl-etanolamid (PEA)
- receptors CB1 a CB2
- CB1 in PAG and RVM, sensory neuron
- CB2 in structures of immune system
- FAAH – hydrolasis of FA amids
Types of pain, phenomenology (2)
(Head zones) Referred pain

- Diaphragm (C4)
- Oesophagus (T4 and T5)
- Liver and gall bladder (T8–T11)
- Colon (T11)
- Bladder (T11–L1)
- Small intestine (T10)
- Stomach (T8)
- Heart (T3 and T4)
- Kidney and testes (T10–L1)
B. Referred Pain

Converging neurons

Infarction

1 Referred pain

Pain sensation

Contusion

2 Projected pain

3 Phantom pain

Referred and pathologic pain

Other pathologic painful sensations:

..., headache, n. trigeminus, Migraine, ...
Localization of CNS pain pathways
Localization of sensory, affective and cognitive pain components
C. Pain Relief

- Anesthesia, alcohol
- Electroacupuncture, transcutaneous nerve stimulation
- Cooling, Na$^+$ channel blocker
- Cooling, PGE synthesis inhibitor
- Morphine
- Central grey matter
- Raphe nuclei
- Associated autonomic reaction, motor response
- Anterior column
- Inhibitory pain tract
- Transsection
- Perception
- Suffering
- Thalamus

23
Motor disorders/
Movement disorders
Movement disorders

- Muscle disorders
- Lower motoneuron disorders
- Upper motoneuron disorders
- Basal ganglia disorders
- Cerebellum disorders
- Passive movement apparatus disorders
Lower motoneuron - Neuromuscular unit disorders
Diseases of the motor unit

A. Diseases of the Motor Unit

1. Amyotrophic lateral sclerosis
   - Spinal muscular atrophy
   - Poliomyelitis
   - Autoimmune
   - Metabolic (B₁, B₁₂ deficiency, diabetes mellitus)

2. Toxic (lead, alcohol)
   - Genetic (Charcot-Marie-Tooth syndrome)

3. Autoimmune
   - Genetic

Death of supraspinal neurons → Hyperreflexia, spasticity
Death of α-motoneurons → Fasciculation
Slowing of conduction velocity, disorders of sensory functions (sensory loss, paresthesias)
Fibrillations
<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Neuropathy</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Loss of reflexes</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Fasciculations (twitchings)</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Sensory deficit</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal reflexes (Babinski)</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>
Lower motoneuron disorders

• Peripheral nerve affected
  – Axonal degeneration; injury → Waller degeneration
  – Axonal demyelinization (Guillain Barre syndrome)

(Both motor and sensory disorder)

• $\alpha$-motoneuron soma affected
  – Inflammation (eg. poliomyelitis)
Lower motoneuron disorders

- (only motor disorders)
  - Motor unit (fasciculations)
  - Atrophia of the whole motor unit
  - When denervated, first comes fibrillation, then atrophia
Upper motoneuron

Is it a
- Pyramidal pathway?
or
- Extra-pyramidal system?
Upper motoneuron, signs

- plegia, paralysis
- spasticity
- cogged wheel sign
- hyperreflexia
- clonus
- abnormal exteroceptive reflexes (Babinski)
- (no atrophy, no fasciculations)
Upper motoneuron, point of view of general practice

“Upper motoneuron” means all descendent motor systems, not only tractus cortico-spinalis

Brain → hemiplegia

Spinal cord → paraplegia, quadriplegia
Upper motoneuron disorders
Spasticity

- Higher resistance towards passive movement, accented with higher velocity (scissor gait)
- Hyper-reflexivity
- Central spasticity (abnormal excitation)
- Spinal spasticity (interneurons)
  - Flexor reflexes
  - Extensor spasm (fragment of locomotion?)
  - Sensory neurons
## Spinal shock in man

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time</th>
<th>Physical exam finding</th>
<th>Underlying physiological event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-1d</td>
<td>Areflexia/Hyporeflexia</td>
<td>Loss of descending facilitation</td>
</tr>
<tr>
<td>2</td>
<td>1-3d</td>
<td>Initial reflex return</td>
<td>Denervation supersensitivity</td>
</tr>
<tr>
<td>3</td>
<td>1-4w</td>
<td>Hyperreflexia (initial)</td>
<td>Axon-supported synapse growth</td>
</tr>
<tr>
<td>4</td>
<td>1-12m</td>
<td>Hyperreflexia, Spasticity</td>
<td>Soma-supported synapse growth</td>
</tr>
</tbody>
</table>

In both **meningeal irritation** and **spinal shock** extensor systems take over flexor systems.
CNS trauma.
Spinal Cord Injury (SCI).
Comparison of CNS to PNS (peripheral nerve) injury
Progression of CNS injury (Spinal cord as a model)

- Local swelling at the site of injury which pinches off blood perfusion → ischemia
- Excessive release of glutamate and excitotoxicity of neurons and oligodendrocytes at the site of injury
- Infiltration by immune cells (microglia, neutrophils)
- Free radical toxicity
- Apoptosis/necrosis
Pathophysiology

- **Common Sites**
  - C5-6 and T12 ---- L1
- higher the injury, the greater the motor/sensory loss: refer to syllabi/dermatomes
- **neuro dysfunction depends on the level of the injury**
  - T1 or above QUAD (tetraplegia)
  - T2 or below PARA
  - Above C4 Resp. Paralysis
Pathophysiology (Extent of Injury)

**Complete**
- Loss of voluntary movement/sensation below the injury
- Reflex activity below level of lesion may return after spinal shock resolves
- Worse prognosis for recovery--

**Incomplete**
- (1) Varying degrees of motor/sensory loss below the level of injury & (2) central, lateral, posterior injury
- Three types
  - Central Cord
  - Brown-Sequard
  - Anterior Cord
Incomplete SCI  BROWN-SEQUARD
(cord hemi-section)

On same side as injury--
loss of motor, touch,
pressure, vibration
BUT, pain/tempr intact

On opposite side of
injury--loss of
pain/tempr BUT,
motor, touch, sensory
vibration intact

Cause: __________________________
______________________________
Incomplete SCI  ANTERIOR

loss of motor, pain/temp

mixed sensory loss
touch, proprioception,
vibration remains intact

Cause: ________________
______________
Incomplete SCI
conus medullaris/cauda equina

◆ Compression of lumbar-sacral area
  ◆ Conus T11-L1
  ◆ Cauda L2-sacral
◆ Better prognosis because injury in “horse tail” area
◆ Loss of motor is variable
◆ Sensory unimpaired
◆ Flaccid bowel and bladder
◆ Impaired sexual function
Autonomous urinary bladder