Peripheral neuropathy (PN)

- damage or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected
  - chronic: long term, begins subtly and progresses slowly
  - acute: sudden onset, rapid progress and slow resolution

- sensory nerves, motor nerves, autonomic nerves
Neuropathy classification

- neuropathy affecting just one nerve is called “mononeuropathy”

- neuropathy involving multiple nerves in roughly the same areas on both sides of the body is called "symmetrical polyneuropathy"

- two or more separate nerves in disparate areas of the body are affected is called "mononeuritis multiplex” or multifocal mononeuropathy" or "multiple mononeuropathy“.

Prevalence of PN

- Osteosclerotic myeloma (POEMS) 50-85%
- WM 30-50%
- MGUS 5-37%
- Amyloidosis (AL) 10-20%
- Cryoglobulinemia 7-15%
- Multiple myeloma 3-14%
- Lymphoma 2-8%
Signs and symptoms

• sensory function “negative” symptoms:
  o numbness to touch and vibration,
  o reduced sensitivity to temperature change and pain,
  o reduced position sense causing poor coordination and balance, and gait abnormality

• sensory function “positive” symptoms:
  o tingling, itching, crawling, pins and needles
  o pain or skin allodynia (severe pain from normally non-painful stimuli, such as light touch).
Signs and symptoms

• motor function “negative” symptoms (loss of function):
  o impaired balance and coordination
  o weakness and tiredness
  o heaviness and gait abnormalities

• motor function “positive” symptoms (gain of function):
  o cramps
  o tremors
  o muscle twitches (fasciculations)
Signs and symptoms

- autonomic nerve dysfunction:
  - poor bladder control
  - abnormal blood pressure or heart rate
  - reduced ability to sweat normally

- pain in the muscles (myalgias)

- Neuropathy may cause muscle loss, bone degeneration, and changes in the skin, hair, and nails.
Mechanism of neuropathy

- Mono, multi, cranial neuropathy & radiculopathy
  - direct infiltration
  - nerve/root compression
  - hyperviscosity
  - bleeding diathesis
  - cryoglobulinemia

- Symmetric polyneuropathy
  - Amyloidosis
  - chemo/drug related toxicity
  - M-protein reactivity with nerve (IgM)
  - unknown
Anti-neural antigens of IgM

<table>
<thead>
<tr>
<th>Antigens</th>
<th>% PN</th>
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<tbody>
<tr>
<td>MAG</td>
<td>50%</td>
</tr>
<tr>
<td>Sulfatide</td>
<td>6%</td>
</tr>
<tr>
<td>GQ1b+Disyalo</td>
<td>2%</td>
</tr>
<tr>
<td>GD1a</td>
<td>3%</td>
</tr>
<tr>
<td>GM2</td>
<td>2%</td>
</tr>
<tr>
<td>GM1</td>
<td>&lt;2%</td>
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TREATMENT OF PN

• *Patients not impaired in their daily life:*
  o symptomatic therapy for tremor and paresthesias
  o reassurance on the usually good prognosis for several years

• *Slightly impaired patients:*
  o due to its safe profile and efficacy plasma exchange is probably preferred as first line treatment or during worsening / flare-ups

• *Moderately impaired patients:*
  o Immunotherapy and/or chemo therapy
  o Rituximab is currently probably the preferred 1st line option.
Therapy of anti-MAG IgM PN

- Rituximab (62%)
- Plasma exchange (45%)
- Chlorambucil (40%)
- Steroids (39%)
- Cyclophosphamide (47%)
- IVIg (18%)
- Interferon α (27%)
- Fludarabine (52%)
- Other therapies (14%)
Immunotherapy for anti-MAG IgM PN

The Cochrane Library Reviewers’ conclusions:

• There is inadequate reliable evidence from trials of immunotherapies in anti-MAG neuropathy to recommend any particular immunotherapy.

• IVIg is relatively safe and may produce some short-term benefit.

• Large randomized trials of at least 12 months duration are required to assess the efficacy of existing or novel therapies.
PAIN

- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.

- Chronic pain is a complex phenomenon where the intensity and impact of the pain is not always directly related to pathology.
Treatment strategy

- the underlying cause of pain should be treated whenever possible
- oral medicines are key components of pain management
- some medicines should be given regularly ("by the clock")
- therapeutic regimes need to be individualized
- monitor and evaluate for therapeutic and side effects
The Chronic Pain Treatment Continuum

- **Diagnosis**
  - Physical Therapy
  - OTC Pain Medications

- **First-Tier Pain Therapies**
  - NSAIDs
  - TENS
  - Psychological Therapy
  - Nerve Blocks

- **Second-Tier Pain Therapies**
  - Opioids
  - Neurolysis
  - Thermal Procedures

- **Advanced Pain Therapies**
  - Neurostimulation
  - Implantable Drug Pumps
  - Surgical Intervention
  - Neuroablation
Pharmacological therapy

- anticonvulsants
- antidepressants
- benzodiazepines
- \( N \)-methyl-d-aspartate (NMDA) receptor antagonists
- nonsteroidal anti inflammatory drugs (NSAIDs)
- opioid therapy
- topical agents
Opioid therapy

- controlled or extended release opioid therapy (e.g., morphine and oxycodone) provides effective pain relief for patients with neuropathic pain
- side effects: nausea or vomiting, constipation, dizziness, somnolence, and pruritus
- morphine, codeine, hydrocodone, oxycodone, buprenorphine, fentanyl, methadone, tramadol, etc ...
New therapies?

- research done between 2005 and 2010 indicates that synthetic cannabinoids and inhaled cannabis are effective treatments for a range of neuropathic disorders
- opiate derivatives taken orally were found to be more effective than cannabis for most people
- smoked cannabis was found to relieve neuropathy associated with HIV-associated sensory neuropathy, CRPS type I, spinal cord injury, peripheral neuropathy, and nerve injury
- combination therapy with opioids and cannabinoids found to be synergistic in many studies from Israel
Individualized therapy

- we are all different in many respects and patients who suffer from PN will need to try numerous combinations of therapies before finding the one that works well to control symptoms.

- the underlying cause of pain should be treated whenever possible and safe to do so.
Questions for the doctor

• What is the evidence for the use of older medications as compared to newer ones order to achieve rapid, effective and safe pain control?
• What is the evidence for the use of second generation anti-epileptics (gabapentin) as compared to first generation anti-epileptics (carbamezapine) in order to achieve rapid, effective and safe pain control?
• What is the evidence for the use of second generation anti-epileptics such as gabapentin as compared to placebo in order to achieve rapid, effective and safe pain control?