Peripheral neuropathy (PN)

- damage or disease affecting nerves, which may impair sensation, movement, gland or organ function
  - chronic: long term, begins subtly and progresses slowly
  - acute: sudden onset, rapid progress and slow resolution
- sensory nerves, motor nerves, autonomic nerves
Peripheral neuropathy (PN)

- The peripheral nervous system sends information from your brain and spinal cord (central nervous system) to the rest of your body.

- Peripheral neuropathy (damage to your peripheral nerves) can cause weakness, numbness and pain, usually in your hands and feet. It can also affect other areas of your body.

- Variable clinical presentation.
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:
  o poor bladder control
  o abnormal blood pressure or heart rate
  o 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.
Prevalence of PN

- Paraproteinemic neuropathies (single monoclonal gammaglobulin)
  - 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%
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>Anti-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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</tbody>
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Diagnosis of PN

• History and physical exam

• Initial labs: CBC; Renal & Liver function; Bone chemistry; B2 microglobulin; LDH; NT-proBNP; Cryoglobulin testing; Serum free light chains; SPEP; Immunofixation; HIV serology; Hepatitis B & C serology; Urinalysis including UPEP; Bone marrow biopsy; CT chest, abdomen, pelvis

• Other labs: serum B12 and folate; HGA1C; Anti-mag antibodies; Anti-ganglioside antibodies; Lyme disease serology; CSF; EMG; nerve biopsy
Nerve Conduction Studies

- **EMG (electromyography) recommendations:**
  - Use to clarify the nature of the neuropathy and expand or curtail investigation;
  - Clinicians need to be very clear to request specific answers to questions when ordering the test;
  - Results of the EMG need to be viewed in context with the clinical picture of PN;
  - Minimize risks to the patient (pacemaker, defibrillator, etc...).
Treatment of PN

• Patients not impaired in their daily life:
  o symptomatic therapy for tremor and paresthesias

• Significant of progressive disease:
  o Immunosuppressive or immunomodulatory treatment: rituximab and/or rituximab combinations, and then second line agents
  o Watch for IgM flare – plasma exchange?
  o IVIG, steroids, plasma exchange of little use according to newer recommendations.
  o Avoid neurotoxic agents
Therapy of anti-MAG IgM PN

- Past treatment examples:
  - Rituximab (62%)
  - Plasma exchange (45%)
  - Chlorambucil (40%)
  - Steroids (39%)
  - Cyclophosphamide (47%)
  - IVIG (18%)
  - Interferon α (27%)
  - Fludarabine (52%)
  - Other therapies (14%)
Pain symptoms

• 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
• Nerve stimulators, nerve blocks
Pharmacological therapy

- anticonvulsants
- antidepressants
- benzodiazepines
- $N$-methyl-$d$-aspartate (NMDA) receptor antagonists
- nonsteroidal anti inflammatory drugs (NSAIDs)
- opioid therapy
- cannabinoids
- topical agents
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.
Reference Article

- 8th International Workshop in Waldenstrom Macroglobulinemia (IWWM8) reference article:
  - Investigation and management of IgM and Waldenstrom-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel
  - British Journal of Haematology; guideline. 2017; doi:10.1111/bjh.14492