NEUROPATHY IN WALDENSTROM MACROGLOBULINEMIA

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OUTLINE

• Anatomy
• Epidemiology
• Types
• Pathophysiology
• Investigation
• Treatment
DEFINITION - NEUROPATHY

• a condition that develops from disease or damage to the **peripheral** nervous system — the vast network that transmits information between the central nervous system (the brain and spinal cord) and every other part of the body.— [NINDS NIH]

• Symptoms - numbness or tingling, pricking sensations (paresthesia) or weakness.

• burning pain (especially at night), muscle wasting

• **Peripheral** (or distal) refers to the areas furthest from the body or core
MOTOR PATHWAYS

https://medatrio.com/ascending-descending-tracts-of-spinal-cord/
PAIN AND TEMPERATURE PATHWAYS

FIGURE 17. The central nervous system pathways that mediate the sensations of pain and temperature.
POSITION SENSE AND BALANCE PATHWAYS
ORIGIN OF THE PERIPHERAL NERVE

Spinal cord

Dorsal root (= posterior) root

Dorsal root ganglion

Dorsal primary ramus (to skin and muscles of back)

Spinal nerve

Ventral primary ramus

Sensory fiber

Postganglionic sympathetic innervation (glands, blood vessels)

Gray ramus communicans

Ventral (= anterior) root

White ramus communicans

Sympathetic (paravertebral) ganglion

Motor axon (to skeletal muscle)
EPIDEMIOLGY

• Precision limited given multiple different definitions & causes & reporting
• Peripheral neuropathy affects at least 20 million people in the United States
• Neuropathy is reported in 50% of patients with diabetes mellitus
• Guillain Barre Syndrome 1.5 cases/100,000/year, for example
• Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) affects 5 people in every 100,000 (if population of Seattle is 800,000, then roughly 40 people in Seattle have THIS type of neuropathy)
• Starbucks has 23 coffee shops for every 100,000 residents in Seattle
HOW TO APPROACH PERIPHERAL NEUROPATHY

• What is the distribution?
• Which fiber types are involved?
• What is the temporal profile?
• Axonal vs demyelinating?
• Symptom type Sensory vs motor (weakness)?
<table>
<thead>
<tr>
<th>Neuropathy type</th>
<th>Distribution</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mononeuropathy</td>
<td>Single nerve</td>
<td>+/-</td>
</tr>
<tr>
<td>Eg carpal tunnel syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
<td>Multiple non-contiguous nerves</td>
<td>Usually</td>
</tr>
<tr>
<td>Length-dependent sensorimotor polyneuropathy (SMPN)</td>
<td><strong>Distal</strong> – feet then hands/symm</td>
<td>+/-</td>
</tr>
<tr>
<td>CIDP (Chronic Demyelinating)</td>
<td>Distal – sensory</td>
<td>uncommon</td>
</tr>
<tr>
<td></td>
<td>Proximal - weakness</td>
<td></td>
</tr>
</tbody>
</table>
POLYNEUROPATHY - CAUSES

- Compressive (mononeuropathies)
- Hereditary
- Associated with systemic disease
- Infectious
- Inflammatory
- Immune mediated
- Toxic
- Associated with neoplasm (cancer)
IMMUNE-MEDIATED

• Paraprotein = monoclonal component = monoclonal gammopathy
• Paraproteinemic neuropathy
  • Monoclonal gammopathy of undetermined significance (MGUS) 5-10%
  • IgM 50% - ½ with antiMAG
  • IgA & G – many axonal and poorly responsive to therapy
• Primary systemic amyloidosis
  • Painful sensory neuropathy
  • Autonomic symptoms
  • Males after the 6th decade
  • Biopsy-nerve +/- rectum, fat pad
INVESTIGATION
IDENTIFICATION AND EVALUATION

- Laboratory tests
- Nerve Conduction Study
  - Demyelinating
  - Axonal
  - Distribution
  - Severity
- Nerve biopsy
EVALUATION - LABORATORY TESTS

• AAN practice guidelines minimal testing:
  • Vitamin B12, serum protein electrophoresis (SPEP), Glucose

• Rare, based on potential cause
  • Metabolic – kidney and liver function, thyroid
  • Inflammatory – ANA, ESR, CRP
  • Heavy metal - Hg, As, Pb – 24 hour urine
  • Paraneoplastic – anti Hu, anti CRMP5

• Genetics – DNA testing for inherited causes
EVALUATION CONT.

• Nutritional (in addition to vitamin B12 deficiency
  • Assess EtOH intake
  • folate
  • Vitamin E
  • excess vitamin B6

• Medications
  • Chemotherapy
  • Amiodarone, metronidazole, HIV meds, Antabuse

• Immune-mediated
  • Paraproteinemic = monoclonal gammopathy
FEATURES - NERVE CONDUCTION STUDY

- Normal

- Axonal Reduced nerve action potential amplitudes

- Slowed conduction velocity

- Temporal dispersion
NERVE CONDUCTION-F WAVES-
DEMYELINATING

Normal

Slowed conduction
OTHER INVESTIGATIONS NERVE BIOPSY
Axonal = underlying nerve affected
^axon loss, severe

<-axon loss, moderate

Myelinated axon loss ->
CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

- Progressive over at least 2 months
- Symmetric proximal and distal weakness, distal more common
- Sensory involvement in 80%
- Decreased deep tendon reflexes
- Immune mediated – relapses
TREATMENT
TREATMENT

• Treat underlying cause

• Supportive – orthoses, balance training

• Neuropathic pain medication
  • Eg gabapentin, amitriptyline, pregabalin, duloxetine, venlafaxine
LINK BETWEEN NEUROPATHY AND WALDENSTROMS
MONOCLONAL GAMMOPATHY (MGUS)

• An age-related condition where bone marrow plasma cells accumulate and overproduce protein (without malignant/cancer cells)

• 3 criteria:
  • monoclonal paraprotein less than 3 g/dL;
  • plasma cells less than 10% in bone marrow;
  • no bone lesions, anemia, high calcium or kidney failure

• 10 % of patients with a neuropathy of unknown origin have a monoclonal gammopathy (MGUS)

• Paraprotein = monoclonal component; paraproteinemnia = monoclonal gammopathy
Pathogenesis of MGUS and its progression
Plasma cell (a differentiated form of B cells) proliferation – these secrete antibodies (IgM, IgG, IgA) in excess = paraproteinemia
MONOCLONAL PROTEINS

Proteins are heavy chains and light chains

-Heavy chain subtypes (IgG, IgA, IgM, and less commonly IgD or IgE)
  \( \text{IgG} = \text{immunoglobulin gamma} \)
  \( [\text{M is mu or macroglobulin, A is beta 2 a globulin or alpha}] \)

-Light chain subtypes (kappa or lambda)

-Gammopathy is (too much) immunoglobulin in the blood

NEUROPATHY SYMPTOMS

• Neuropathy symptoms: foot numbness, paresthesias, imbalance, dysesthesia (painful sensations)

• Early stages, generally - abnormal sensation in the legs in large fibers (touch, joint position, vibration)

• With progression, weakness in distal muscles with variable atrophy
PARAPROTEINEMIC NEUROPATHY

• a heterogeneous set of neuropathies
• characterized by the presence of homogeneous immunoglobulin
• Paraproteins = an abnormal clonal proliferation of B-lymphocytes or plasma cells produces the immunoglobulins in excess
• may or may not occur in the context of a hematologic malignancy
• Paraproteins are detected in the serum of approximately 1 % of the general population
• & in up to 5.3 % over 70 years and up to 10 % over 80 years
MYELIN ASSOCIATED GLYCOPROTEIN (MAG)

• A specific protein
• Antibody to MAG; IgM gammopathy
• More common in males
• Usually >50 years old
• Balance and walking difficulties due to numbness
• Weakness often mild
• Tremor 30%
ANTI-MAG NEUROPATHY

• sensory and motor neuropathy

• “distal acquired demyelinating symmetric” (DADS)

• usually slowly progressive & little functional deterioration over time;

• one report (n=140) showed that 10 and 15 years after onset, 24 % and 50 % of patients were disabled
# IMMUNOGLOBULIN (IG) HEAVY CHAIN CLASS

<table>
<thead>
<tr>
<th>Patient group (%)</th>
<th>IgG</th>
<th>IgM</th>
<th>IgA</th>
<th>IgD</th>
<th>Biclonal</th>
<th>Light chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>All M-proteins</td>
<td>70</td>
<td>15</td>
<td>12</td>
<td>&lt; 1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Polyneuropathy &amp; MGUS</td>
<td>35</td>
<td>50</td>
<td>12</td>
<td></td>
<td>3</td>
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</tr>
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</table>
PATIENTS WITH IGM TYPE OF MG

• MGUS (42%) – monoclonal gammopathy of undetermined significance
• Waldenstrom (WM, 30%); if IgM HIGH - >80% likely WM
• B cell non-Hodgkin's lymphoma (18%)
• Primary cold agglutinin disease (pCAD, 4%)
• Primary amyloidosis (4%)
• Cryoglobulinemia (2%)
• IgM MGUS associated neuropathy (2%)
• multiple myeloma (0.8%), and POEMS (0.5%)
Fig. 1. The levels of serum IgM in different diseases. WM, Waldenstrom macroglobulinemia; sWM, smoldering Waldenstrom macroglobulinemia; MM, multiple myeloma; pCAD, primary cold agglutinin disease; AL, amyloidosis; PN, peripheral neuropathy; POEMS, etc

DISEASE TYPES OF IGM

• **Kappa** type light chain indicated the diagnosis of Waldenstroms, pCAD, IgM MGUS associated neuropathy and cryoglobulinemia

• **Lambda** type light chain indicated POEMS and amyloidosis

• 25% with ‘unrelated’ autoimmune diseases
### Motor Nerve Conduction Studies:

<table>
<thead>
<tr>
<th>Nerve and Stimulus Site</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Area (mVms)</th>
<th>Duration (ms)</th>
<th>Segment</th>
<th>Latency diff. (ms)</th>
<th>Distance (mm)</th>
<th>Conduction velocity (m/s)</th>
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<tbody>
<tr>
<td><strong>Median R</strong></td>
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<td>(Temperature: 32.6 °C)</td>
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<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>6.2*</td>
<td>13.0</td>
<td>48.4</td>
<td>7.9</td>
<td>APB-Wrist</td>
<td>6.2</td>
<td>80</td>
<td>46</td>
</tr>
<tr>
<td>Elbow</td>
<td>11.6</td>
<td>11.5</td>
<td>48.0</td>
<td>8.7</td>
<td>Wrist-Elbow</td>
<td>5.4</td>
<td>250</td>
<td>46</td>
</tr>
<tr>
<td>Axilla</td>
<td>15.1</td>
<td>10.5</td>
<td>51.5</td>
<td>8.9</td>
<td>Elbow-Axilla</td>
<td>3.5</td>
<td>140</td>
<td>40</td>
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<tr>
<td><strong>Ulnar L</strong></td>
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</tr>
<tr>
<td>Wrist</td>
<td>4.8*</td>
<td>12.1</td>
<td>53.5</td>
<td>7.7</td>
<td>Abductor digiti minimi (manus)-Wrist</td>
<td>4.8</td>
<td>80</td>
<td>49</td>
</tr>
<tr>
<td>Below elbow</td>
<td>9.1</td>
<td>11.3</td>
<td>50.7</td>
<td>7.6</td>
<td>Wrist-Below elbow</td>
<td>4.3</td>
<td>210</td>
<td>49</td>
</tr>
<tr>
<td>Above elbow</td>
<td>12.4</td>
<td>9.7</td>
<td>49.0</td>
<td>8.3</td>
<td>Below elbow-Above elbow</td>
<td>3.3</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Axilla</td>
<td>15.0</td>
<td>9.0</td>
<td>44.6</td>
<td>8.2</td>
<td>Above elbow-Axilla</td>
<td>2.6</td>
<td>140</td>
<td>54</td>
</tr>
<tr>
<td><strong>Peroneal R</strong></td>
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<td>(Temperature: 27.2 °C)</td>
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<td>(Temperature: 27.2 °C)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>20.9*</td>
<td>0.3*</td>
<td></td>
<td></td>
<td>Ext dig brevis-Ankle</td>
<td>20.9</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Fibular head</td>
<td>52.7</td>
<td>0.5</td>
<td></td>
<td></td>
<td>Ankle-Fibular head</td>
<td>31.8</td>
<td>335</td>
<td>11</td>
</tr>
<tr>
<td>Knee</td>
<td>57.4</td>
<td>0.6</td>
<td></td>
<td></td>
<td>Fibular head-Knee</td>
<td>4.7</td>
<td>100</td>
<td>21</td>
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<tr>
<td><strong>Tibial R</strong></td>
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<td>(Temperature: 28.6 °C)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td>Abductor hallucis-Ankle</td>
<td>120</td>
<td>300</td>
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</table>
### Peroneal L
(Mean temperature: 28.2 °C)

<table>
<thead>
<tr>
<th>Location</th>
<th>Temp (°C)</th>
<th>Latency (ms)</th>
<th>Amplitude (µV)</th>
<th>Segment</th>
<th>Latency difference (ms)</th>
<th>Distance (mm)</th>
<th>Conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle</td>
<td>19.1*</td>
<td>0.1</td>
<td>4.8</td>
<td>Ext dig brevis-Ankle</td>
<td>19.1</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Fibular head</td>
<td>39.0</td>
<td>0.5</td>
<td>6.5</td>
<td>Ankle-Fibular head</td>
<td>19.9</td>
<td>340</td>
<td></td>
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</tbody>
</table>

**Tibial L**
(Mean temperature: 28.5 °C)

<table>
<thead>
<tr>
<th>Location</th>
<th>Temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle</td>
<td></td>
</tr>
</tbody>
</table>

**F-waves**: (Height: 72”)

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Latency (ms)</th>
<th>Persistence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median R</td>
<td>36.9</td>
<td>10/16</td>
</tr>
<tr>
<td>Ulnar R</td>
<td>39.3</td>
<td>7 of 10</td>
</tr>
</tbody>
</table>

### Sensory Nerve Conduction Studies:

<table>
<thead>
<tr>
<th>Nerve and Stimulation Site</th>
<th>Onset latency (ms)</th>
<th>Peak latency (ms)</th>
<th>Amplitude (µV)</th>
<th>Temp</th>
<th>Segment</th>
<th>Latency difference (ms)</th>
<th>Distance (mm)</th>
<th>Conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median R</td>
<td>3.8</td>
<td>4.8</td>
<td>4.1*</td>
<td>31.5°C</td>
<td>Index-Wrist</td>
<td>3.8</td>
<td>140</td>
<td>37*</td>
</tr>
<tr>
<td>Wrist</td>
<td>3.8</td>
<td>4.7</td>
<td>5.0*</td>
<td>31.4°C</td>
<td>D 5-Wrist</td>
<td>3.8</td>
<td>140</td>
<td>37*</td>
</tr>
<tr>
<td>Ulnar R</td>
<td>4.6</td>
<td>5.5</td>
<td>5.0*</td>
<td>28.0°C</td>
<td>Ankle-Calf</td>
<td>4.6</td>
<td>140</td>
<td>31*</td>
</tr>
<tr>
<td>Wrist</td>
<td>4.5</td>
<td>5.7</td>
<td>3.3*</td>
<td>32.8°C</td>
<td>Ankle-Calf</td>
<td>4.5</td>
<td>140</td>
<td>31*</td>
</tr>
</tbody>
</table>
• SGPG, Elisa: 204800 (Positive)
• MAG, Elisa: 204800 (Positive)
• MAG, Western Blot: (Positive)
WALDENSTROM MACROGLOBULINEMIA (WM)

- Peripheral neuropathy in 5-30%, 1 report up to 47% of patients
- Most patients - sensory loss & unsteady gait
- Less commonly - predominant motor neuropathy, may be associated with elevated IgM antibodies targeting ganglioside GM1

\[
\begin{align*}
\text{Gal}^\beta_1\text{-3GalNAc}^\beta_1\text{-4Gal}^\beta_1\text{-4Glc}^\beta_1\text{-1′Ceramide} \\
\text{Neu5Ac}^\alpha_2 \\
\text{GM1 ganglioside}
\end{align*}
\]
WALDENSTRÖM’S MACROGLOBULINEMIA (WM)

• associated with neuropathy – axonal or demyelinating or other forms
• neuropathy is associated with IgM kappa - with or without anti-MAG
• Neuropathy in WM looks like IgM MGUS-neuropathy with anti-MAG antibodies
• Nerve conduction studies show demyelination in some
• pathologic studies show widening of lamellae like in IgM MGUS
• the neuropathy of WM is likely dependent on the IgM paraprotein type
TREATMENT

• General immune neuropathy/CIDP
  • Steroids
  • IVIG
  • Plasma exchange (PE) with or without cyclophosphamide

• WM
  • Rituximab
  • Decadron, rituximab, cyclophosphamide (DRC)
  • PE
TREATMENT

• consider treatment (always in consultation with a hematologist) when the monoclonal protein rises above a concentration of 1.5 g/dL

• severity, progression, and degree of motor deficit determine treatment

• Immune therapies – studies group different types of neuropathy

• Treatment decisions are complicated by limited numbers of like neuropathy
IVIG – INTRAVENOUS IMMUNOGLOBULIN

• short-term benefit in 50 % with IgM paraprotein neuropathies (anti-MAG in half)
• 0/7 trials w/ adequate evidence to support immunotherapies based on 2 disability measures
• 2 short trials of IVIG showed statistically significant improvements 2 measures: Modified Rankin Scale (disability) at 2 weeks and 10-m walk time at 4 weeks
• Other small studies have indicated that IVIg was effective in 15 to 20 % of patients
PLASMA EXCHANGE (PE)

• separates blood cells from plasma, returns purified blood, diluted with a plasma substitute, to the circulation

• only short term efficacy and must be repeated to maintain effectiveness

• limited utility for treatment of IgM-associated “paraproteinemic” neuropathy (=MGUS neuropathy!)

• systematic review for IgG or IgA PPN – modestly better short-term
CONSENSUS STATEMENT (IWWM-7)

• “Therapeutic strategy in WM should be based on individual patient and disease characteristics (age, comorbidities, need for rapid disease control, candidacy for autologous transplantation, cytopenias, IgM-related complications, hyperviscosity and neuropathy).

• Mature data show that rituximab combinations with cyclophosphamide/dexamethasone, bendamustine, or bortezomib/dexamethasone provided durable responses and are indicated for most patients.”
WALDENSTROM NEUROPATHY TREATMENT

- plasmapheresis, in aggressive neuropathy; should not be used permanently
- rituximab resulted in improved sensory function in several studies, including a placebo-controlled trial – good for mild cases
- moderate to severe IgM neuropathy, data indicate more rapid improvement with the fludarabine-rituximab combination than with rituximab alone
- Dexamethasone, rituximab, cyclophosphamide less toxic
RITUXIMAB

• Monoclonal antibody targeting CD20 antigen on B lymphocytes
• 30% improved in robust trial - demyelinating neuropathy, an IgM monoclonal protein, anti-MAG vs placebo
• One review – IgM MGUS (75%) and IgM WM - responders in MGUS (56%) and WM (44%), only 33 patients
• Up to 80% improvement in IgM neuropathy with +MAG (retrospective)
CYCLOPHOSPHAMIDE

• 35 pts IgM MGUS –
• 6 months oral treatment + prednisone
• RCT
• No improvement in functional scales but improved strength
SUMMARY

• Neuropathy is a process in which multiple nerves become diseased or damaged
• There are MANY causes for neuropathy
• The immune system plays a role, specifically in producing too much of a certain type of protein (Monoclonal gammopathy)
• 30-50% of individuals with Waldenstroms Macroglobulinemia develop neuropathy
• Most of these individuals have a demyelinating neuropathy which is mild
• Treatment is determined based on severity and other areas affected
• Rituximab plays a key role in treatment, with most individuals getting improvement in strength more than sensation
• Combination treatments are needed in more aggressive disease
REFERENCES


• Neuromuscular.wustl.edu