Introduction to Peripheral Neuropathy

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Neuropathy

- **Neuropathy**: a functional disturbance and/or pathologic change to the peripheral nervous system
- **Peripheral Nervous System**: includes the nerve roots, the brachial and lumbosacral plexi, and the named nerves in the head, arms and legs
- **Central Nervous System**: brain and spinal cord
Symptoms of PNS dysfunction

- Numbness, tingling
- Loss of sensory modality (s)
- Weakness, atrophy
- Fasciculations

Symptoms of CNS dysfunction:
Numbness, tingling, sensory changes, weakness, (hemi sensory or motor loss) paraplegia, quadriplegia, sensory level, mental status changes, tremor, ataxia, speech changes

PNS vs CNS examination

- **PNS Exam**
  - Reflexes ↓
  - Tone ↓
  - Toes ↓
  - Distribution
    - Distal to proximal
    - Gradient
    - Named nerve

- **CNS Exam**
  - Reflexes ↑
  - Tone ↑
  - Toes ↑
  - Distribution
    - Hemiparesis or sensory loss
    - Quadriplegia or paraplegia
Neuropathy evaluation

- History:
  - Symptoms:
    - Duration or time course
    - Distribution
    - Sensory and/or motor
  - Medical History
  - Family History
  - Occupation/exposures

Time Course of Neuropathy

- Acute: <1 week
  - GBS, Injury
- Subacute: few weeks to few months
  - CIDP, vasculitis, toxins, hereditary, repetitive injury
- Chronic: > few months
  - CIDP, hereditary, toxic, metabolic, idiopathic, autoimmune
Distribution

- Distal length dependent
  - Stocking glove (length dependent neuropathy)
  - Small fiber vs large fiber (or both)
- Asymmetry vs symmetry
- Mononeuropathy
- Multiple mononeuropathies
- Proximal neuropathy vs plexus
- Radiculopathy
- Myeloneuropathy (spinal cord and peripheral)

Past Medical History

- Chronic illnesses
  - Diabetes, thyroid disease, renal dysfunction
  - Autoimmune diseases
  - Malnutrition
  - Malignancy
    - Type - Is there a paraneoplastic association
    - Chemotherapy
  - Medications
    - Neurotoxicity
      - Antibiotics
      - Chemotherapeutic agents
      - Anti-arrhythmic agents
      - OTC agents
Family History

- Similar symptoms
- Difficulty walking
- “Funny Feet”
  - Pes cavus
  - Hammer toes

Images: Diagnosis and Management of Peripheral Nerve disorders, Mendell, JR, Kissel, JT and Cornblath, DR, Oxford University press, 2001

Social History

- Alcohol and other substance abuse
- Heavy metals, nitrous oxide, hydrocarbons, solvents
- Repetitive actions
Neuropathy work up

- Neurologic exam
- Blood Work
- NCV/EMG
- Nerve biopsy
- Imaging

Neurologic Exam : Sensory

- Pattern of abnormality
  - Length dependent
  - Named nerve
  - Multiple nerves

- Modality
  - Large fiber
    - Vibration, position
  - Small fiber
    - Temperature, pin, light touch

Image: Diagnosis and Management of Peripheral Nerve disorders, Mendell, JR, Kissel, JT and Cornblath, DR, oxford University press, 2001
Neurologic Exam: Motor

- Bulk
  - Atrophy
  - Strength
- Reflexes
  - Hypoactive
  - Absent


Neuropathy w/u:

- Metabolic:
  - Glucose, ***glucose tolerance test***, HgbA1c
  - BUN/Cr
  - B6/B12/Folate (MMA and Homocysteine)
  - Cu, Ceruloplasmin
- Quantitative Immunoglobulins and immunofixation (serum free light chains)
- TFTS
- FTA or syphilis evaluation?
- Autoimmune w/u?
- Paraneoplastic evaluation?
# Neuropathy work up

- **Nerve conduction/EMG**
  - Defines neuropathy distribution and extent
  - Differentiates between demyelination and axonal degeneration
  - May reveal subclinical abnormalities
  - May define chronicity

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# Nerve conduction studies

- **Limitations**
  - Findings do not reflect small fiber dysfunction (pain, light touch-
    Quantitative sensory testing, autonomic reflex testing, skin biopsy for intraepidermal nerve fiber densities)
  - Normal findings when sensory loss is due to central nervous system dysfunction (brain and spinal cord)
  - May take 2-4 weeks to detect an abnormality from an acute lesion (wallerian degeneration)
**EMG**

- Muscle is the “end-organ” of motor nerves
- EMG measures the electrical activity of muscle at rest and during contraction
- Muscle electrical activity changes after injury to the innervating nerve
- Thus, knowledge of peripheral nerve and root innervation can further localize site of injury

**Neuropathy w/u**

- Nerve biopsies:
  - Limited utility:
    - Inflammation (vasculitis)
    - Amyloid
  - Specialized lab
  - Experience in performing biopsy
**Neuropathy w/u**

- **Imaging:**
  - MRI, CT/myelogram: define nerve root injury
  - Plain CT: limited utility
  - MRI: peripheral nerve and plexus
  - Ultrasound: focal lesions, nerve swelling

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**Neuropathy**

- Neuropathies can be defined by anatomy
  - Distal length dependent
  - Focal or mononeuropathy
    - Entrapments
    - Direct injuries
    - Radiculopathies
  - Multiple mononeuropathies
  - Proximal neuropathy vs plexus
  - Myeloneuropathy (spinal and peripheral nerve involvement)

- Neuropathies can be defined by pathology
  - Axonal- damage to the axons
  - Demyelinating- myelin impairment
Distal axonopathies (length dependent)

- Distal to proximal gradient
- Symptoms begin in toes: numbness and tingling
- Process marches up and later affects arms
- Sensory and motor both affected with preferential
- Reflexes lost in distal extremities

Distal Axonopathies
Dying-Back / Length-Dependent

- Longest and largest axons affected at the nerve terminal
- Metabolic abnormality affects the cell body and nutrients / cytoskeletal proteins not transported
- Common causes include diabetes, uremia, alcohol, vitamin deficiency, drug toxicity

Image: courtesy of Tom Targos, 1980
### Focal Neuropathies

<table>
<thead>
<tr>
<th>Nerve entrapments</th>
<th>Median, Ulnar, Radial, Peroneal, Tibial</th>
</tr>
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<tbody>
<tr>
<td>Narrow anatomic pathway</td>
<td>Numbness</td>
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<tr>
<td>Fibrosseous tunnel</td>
<td>Tingling</td>
</tr>
<tr>
<td>Superficial course with little protection</td>
<td>Pain</td>
</tr>
<tr>
<td>Compression:</td>
<td>Weakness</td>
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<tr>
<td>acute, intermittent, repetitive, continuous</td>
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### Radiculopathies

- Compromise of the nerve root
- Sensory and/or motor
- Pain +/-
- Often characterized by radiating dysesthesias
- Weakness in the distribution of the nerve root
- Decreased or absent reflex in distribution of nerve root
Myelinopathies

- INHERITED:
  Charcot-Marie-Tooth neuropathies (CMT)

- ACQUIRED:
  Guillain-Barre syndrome (GBS)
  Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Practical Aspects of Neuropathy

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Disclosure: Discussion includes off-label usages of pharmacologic and non-pharmacologic modalities for treating neuropathic
• How do I categorize this neuropathy?
• What is relevance of pain?
• How do I deal with neuropathic pain?
• What other issues should maintenance care involve?
• Who should be referred?
• What are the “warning signs” of something else?

Case Studies

• 56 yo male
• several months of pain in his feet
• described as burning and stinging with shooting pains going up through his toes
• feels as though he is walking on cotton-balls, no padding on his feet
• Ankle hyporeflexia, stocking loss of pinprick and temperature
• balance worsens when he closes his eyes; subtle loss of toe flexion strength.
- Symmetric versus asymmetric
- Distal versus proximal or both
- Sensory and motor

- **Symmetric, distal weakness, S(+M)**
  - Metabolic (DIABETES, renal/liver disease, vitamin deficiencies)
  - Drugs/toxins (Chemo, HMs, meds)
  - Hereditary (amyloidosis, CMT)

- 57 yo male
- low back pain
- radiation of discomfort down his leg into his toes.
- weakness of right toe extension, ankle dorsiflexion, ankle inversion/eversion
- decreased pin on the anterolateral aspect of the calf and dorsum of the foot
- reflexes preserved.
- Asymmetric, distal or proximal, M+S
  - SINGLE
    - Compressive mononeuropathy
    - Radiculopathy
  - MULTIPLE
    - Vasculitis (mononeuritis multiplex)
    - Polyradiculopathy (infection, inflammation)
    - Plexus

- 54 yo female
- viral URTI 2 weeks prior to symptoms
- c/o 3 days numbness and tingling that began in the feet but has progressed to her hands and face; associated aching, prickly, burning back and limb pain
- associated symmetric weakness in the hands and feet, beginning to involve legs.
- diminished reflexes throughout;
- reduced touch, vibration and position sense at the toes, ankles and fingertips
- weakness of toe and ankle dorsiflexion.
Symmetric, distal and proximal, M+S
- Inflammatory
  - Acute Inflammatory Demyelinating Polyneuropathy (GBS)
  - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

45-yo female
- 3-4 months progressive weakness of the right hand
- “maybe some numbness or tingling”
- pronounced atrophy of intrinsic muscles of the right hand and forearm
- sensation intact to light touch, vibration; slightly diminished to pin over forefinger
- reflexes brisk, especially in the weak, atrophic arm.
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Asymmetric, D>P, motor only
- Motor neuron disease
- Multifocal motor neuropathy with conduction block
- 62 yo female
- numbness and tingling in hands followed by feet; prominent balance difficulties with frequent falls
- diminished touch, pain, temperature; prominent loss of vibration and position sense
- reduced reflexes throughout
- mild generalized weakness
- Balance difficulties prominent in exam

- Symmetric, sensory only, “P>D” (Ganglionopathy)
  - Paraneoplastic (antiHu) sensory neuronopathy
  - Sjogren’s syndrome
  - B6 toxicity
  - HIV
  - Cisplatinum
  - Idiopathic
32 yo HIV+ male
left knee buckling, catches toes on the right, difficulty lifting his right arm above his shoulder
diffuse pain and numbness
multifocal, asymmetric weakness
associated sensory loss in a patchy distribution

**Neuropathies with pain**
Common
- DM, idiopathic small fiber neuropathy

Important
- HIV, vasculitis

Distinctive
- GBS (AIDP)

Unusual
- Toxic, Fabry’s, amyloidosis, infiltrative neoplasms, etc
42 yo female with idiopathic small fiber neuropathy
- Pain bothers her during the day, keeps her up at night
- Pain regimen:
  - Gabapentin 300 mg po bid
  - Hydrocodone/acetaminophen as breakthrough (several times/day)
  - Diphenhydramine for sleep

Evidence based Guideline: Treatment of painful diabetic neuropathy

- Anticonvulsants
  - Level A: Pregabalin (300-600mg/day)
  - Level B: Gabapentin (900-3600 mg/day); sodium valproate (500-1200 mg/day)
  - Level U: Topiramate
  - Level B: Oxcarbazepine, lamotrigine, lacosamide
### Evidence based Guideline: Treatment of painful diabetic neuropathy

**Antidepressants**
- **Level B**: Amitriptyline (25-100mg/day); Venlafaxine (75-225 mg/day); Duloxetine (60-120 mg/day)
- **Level C**: Add venlafaxine to gabapentin for a better response.
- **Level U**: Desipramine, imipramine, fluoxetine, nortriptyline plus fluphenazine.

**Opiates**
- **Level B**: Dextromethorphan (400 mg/day); Morphine sulfate (titrated to 120 mg/day); Tramadol (210 mg/day); Oxycodone (mean 37 mg/day, max 120 mg/day)
**Evidence based Guideline: Treatment of painful diabetic neuropathy**

- **Other pharmacologic agents:**
  - Level B: Capsaicin (0.075% qid); isosorbide dinitrate spray
  - Level C: Lidoderm patch
  - Level U: Vitamins, \( \alpha \)-lipoic acid
  - Level B: Clonidine, pentoxifylline, mexiletine.

- **Nonpharmacologic modalities:**
  - Level B: Percutaneous electrical nerve stimulation, 3-4 times per week
  - Level U: Amitriptyline plus electrotherapy
  - Level B: Electromagnetic field treatment, low intensity laser treatment, Reiki therapy.
Therapeutic adjustment

- Pain regimen:
  - Gabapentin 300 mg po bid
  - Hydrocodone/acetaminophen as breakthrough (several times/day)
  - Diphenhydramine for sleep

- New pain regimen
  - ↑ gabapentin OR, switch to pregabalin
  - Use tramadol as breakthrough
  - Use sedating antidepressant (amitriptyline) for sleep
  - Consider addition of topical
  - Consider use of electrotherapy

- 87 yo male
- Distal, symmetric, axonal neuropathy confirmed by NCS/EMG
- Pain well controlled
- No concerns raised
### Management Issues: AAN Guidelines

- **Warning signs?**
- **Screen for acquired causes**
  - diabetes screening, annual
  - B12 with metabolites, SPEP/IFE
  - Consider appropriate testing/referral in clinical context*
- **Screen and manage EtOH misuse**

### Management Issues: AAN Guidelines

- **Ensure pain controlled***
- **Screen and manage fall risk factors***

**Instruments:**
- EtOH: CAGE, Audit C
- Pain: Graded chronic pain scale
- Falls: Get-Up-and-Go test
<table>
<thead>
<tr>
<th>27 yo female</th>
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<tbody>
<tr>
<td>▪ h/o mild, distal, symmetric sensation loss diagnosed on NCS as idiopathic sensory predominant neuropathy</td>
</tr>
<tr>
<td>▪ h/o bilateral CTS, episode of “rucksack palsy” in past</td>
</tr>
<tr>
<td>▪ acute onset of right hand weakness</td>
</tr>
<tr>
<td>▪ sensation loss involves hand and forearm</td>
</tr>
<tr>
<td>▪ reflexes diminished in weak arm</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>32 yo male</th>
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<tbody>
<tr>
<td>▪ h/o IBS, worsening recently with associated weight loss</td>
</tr>
<tr>
<td>▪ c/o numbness and tingling in his feet</td>
</tr>
<tr>
<td>▪ difficulty climbing ladders, walking narrow scaffold</td>
</tr>
<tr>
<td>▪ distal pin, vibration loss</td>
</tr>
<tr>
<td>▪ difficulty fanning his toes</td>
</tr>
<tr>
<td>▪ absent ankle jerks, diminished knee jerks</td>
</tr>
<tr>
<td>▪ sways when his eyes are closed</td>
</tr>
</tbody>
</table>
When to refer

- At onset, to extend diagnostic evaluation
- Atypical appearance for suspected etiology
- Atypical in course, distribution
- Associated features
  - Systemic disorders
  - Associated symptoms/conditions (weight loss, rash, arthritis, liver disease, idiopathic cardiomyopathy, etc)
  - Family history
- Refractory to treatment
- Clinical concern

- Case 1, HNPP; Case 2, celiac disease.

- 50 yo male
- acute onset of neck pain, numbness and tingling in the hands
- progressive gait difficulty
- urinary incontinence.
76 yo female
Received oxaliplatin for colon cancer
C/o unpleasant paresthesias of the mouth, distal extremities and throat while on drug
Improved after completion of therapy
Later developed sensory ataxia with deteriorating balance
Large fiber sensation loss with relatively preserved strength
Review of history revealed patient taking large doses B vitamins to speed recovery

Warning signs

- Central symptoms/signs
  - UMN
  - Hemiparesis/hemisensory loss, paraparesis
  - Prominent or unexplained urinary symptoms
  - Cognitive changes
- Acute onset
- Rapid progression
- Deviating from expected distribution or severity
- Prominent autonomic involvement