Introduction to Peripheral Neuropathy

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Symptoms of PNS dysfunction

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

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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

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

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- **Central Nervous System:** brain and spinal cord

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

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)

Time Course of Neuropathy

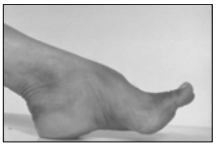
- Acute: <1 week
  - GBS, Injury
- Subacute: few weeks to few months
  - CIDP, vasculitis, toxins, hereditary, repetitive injury
- Chronic: > few months
  - CIDP, hereditary, toxic, metabolic, idiopathic, autoimmune

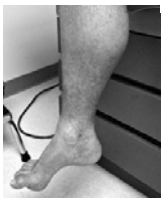
Past Medical History

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

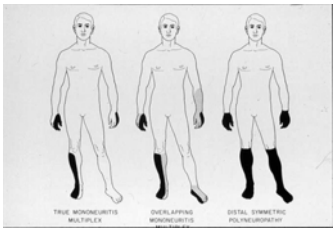
Neuropathy work up

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

Social History

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

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

Image: Entrapment Neuropathies Dawson, DM, Hallett M, Wilbourn AJ 3rd ed.1999 lippincott raven

Neuropathy work up

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

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 syphillis evaluation?
- Autoimmune w/u?
- Paraneoplastic evaluation?

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

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

Neuropathy w/u

- Nerve biopsies:
  - Limited utility:
    - Inflammation (vasculitis)
    - Amyloid
  - Specialized lab
  - Experience in performing biopsy

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

Focal Neuropathies

- Nerve entrapments
  - Narrow anatomic pathway
  - Fibrosseous tunnel
  - Superficial course with little protection
- Compression:
  - acute, intermittent, repetitive, continuous
- Median, Ulnar, Radial, Peroneal, Tibial
  - Numbness
  - Tingling
  - Pain
  - Weakness

Distal Axonopathies
Dying-Back / Length-Dependent

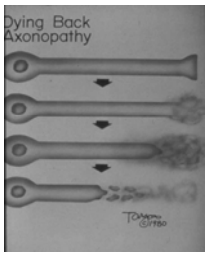


Image: courtesy of Tom Targos, 1980

- 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

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)

- **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?**

Practical Aspects of Neuropathy

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Disclosure: Discussion includes off-label usages of pharmacologic and non-pharmocologic modalities for treating neuropathic

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

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

- <u>Asymmetric, distal or proximal, M+S</u>
  - SINGLE
    - Compressive mononeuropathy
    - Radiculopathy
  - MULTIPLE
    - Vasculitis (mononeuritis multiplex)
    - Polyradiculopathy (infection, inflammation)
    - Plexus

- 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.

- 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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- 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

- <u>Asymmetric, D>P, motor only</u>
  - Motor neuron disease
  - Multifocal motor neuropathy with conduction block

- <u>Symmetric, sensory only, "P>D"</u> (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

- 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

- <u>Neuropathies with pain</u>
  - Common
    - DM, idiopathic small fiber neuropathy
  - Important
    - HIV, vasculitis
  - Distinctive
    - GBS (AIDP)
  - Unusual
    - Toxic, Fabry's, amyloidosis, infiltrative neoplasms, etc

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.

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, α–lipoic acid
  - Level B: Clonidine, pentoxifylline, mexiletine.

Evidence based Guideline: Treatment of painful diabetic neuropathy

- 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

- 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

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

- 87 yo male
- Distal, symmetric, axonal neuropathy confirmed by NCS/EMG
- Pain well controlled
- No concerns raised

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

- 27 yo female
- h/o mild, distal, symmetric sensation loss diagnosed on NCS as idiopathic sensory predominant neuropathy
- h/o bilateral CTS, episode of "rucksack palsy" in past
- acute onset of right hand weakness
- sensation loss involves hand and forearm
- reflexes diminished in weak arm

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.

- 32 yo male
- h/o IBS, worsening recently with associated weight loss
- c/o numbness and tingling in his feet
- difficulty climbing ladders, walking narrow scaffold
- distal pin, vibration loss
- difficulty fanning his toes
- absent ankle jerks, diminished knee jerks
- sways when his eyes are closed

- 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