Outline

- Vasculitic Neuropathies
- Autoimmune Small Fiber Neuropathies
- Sensory Neuronopathies (Dorsal Root Ganglionopathies)
- Other Autoimmune Large Fiber Neuropathies
- Trigeminal Neuropathies
Vasculitic Neuropathy

Definition

- Damage to the peripheral nerves as a consequence of vasculitis

Classic Presentation: Mononeuritis Multiplex

- Inflammation of several separate nerves in unrelated portions of the body

Case #1: 62 Year-old with Numbness, Pain and Weakness

- 62 year-old woman developed ankle edema, streaking of her skin, and malaise
- Developed the following symptoms:
  - right foot paresthesias and numbness
  - spread to the left foot, then right hand, then left hand
  - severe neuropathic pain
  - diffuse weakness and ataxia
  - 10 lb weight loss
62 Year-old with Numbness, Pain and Weakness

On exam:
- Normal cranial nerves
- Motor exam:
  - Normal bulk/tone
  - Bilateral hip flexion 4-/5
  - Left finger extension/abduction/flexion 4/5
  - Decreased pinprick to the wrist and ankle bilaterally
  - Impaired proprioception at the toes and right fingers
- Deep tendon reflexes were normal

### Sensory NCS

<table>
<thead>
<tr>
<th>Nerve / Sites</th>
<th>Rec. Site</th>
<th>Onset ms</th>
<th>Peak ms</th>
<th>NP Amp μV</th>
<th>PP Amp μV</th>
<th>Dist cm</th>
<th>Vel m/s</th>
<th>Temp °C</th>
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<tbody>
<tr>
<td>L MEDIAN - Dig II</td>
<td>Wrist</td>
<td>2.15</td>
<td>3.00</td>
<td>23.5</td>
<td>33.7</td>
<td>13</td>
<td>60.5</td>
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<td>3.30</td>
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<td>52.0</td>
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<td>3.00</td>
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<td>37.4</td>
<td>11</td>
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<tr>
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<td>3.00</td>
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<td>41.1</td>
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<td>NR</td>
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<td>NR</td>
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<tr>
<td>R SURAL - Lat Mall</td>
<td>Calf</td>
<td>Lat Mall</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>14</td>
<td>NR</td>
</tr>
</tbody>
</table>
62 Year-old with Numbness, Pain and Weakness

- Multiple mononeuropathies (mononeuritis multiplex)
- Admit from EMG lab
62 Year-old with Numbness, Pain and Weakness

- TSH 5.8, T4 1.4
- ESR 54 (0-20)
- CRP 5.7 (<0.5)
- HIV nonreactive
- Hep B Ab NEG
- Hep C Ab NEG
- ENA panel NEG

- Myeloperoxidase >8 (nml <1)
- Proteinase 3 NEG
- PPD test negative.

SEVERE NECROTIZING VASCULITIC NEUROPATHY DUE TO MICROSCOPIC POLYANGIITIS

62 Year-old with Numbness, Pain and Weakness

- Started on 60 mg of prednisone
- Started rituximab induction 375 mg/m² x 4 weeks
- Gabapentin
- Azathioprine

Classification Schemes

1. 2012 International Chapel Hill Consensus Conference
2. Peripheral Nerve Society Task Force classification
   - Primary Systemic Vasculitides
   - Secondary Systemic Vasculitides
   - Non-systemic/localized Vasculitides
3. Based on size of involved vessel
   - Nerve Large Arteriole
   - Microvasculitis
Specific Forms of Vasculitic Neuropathies

- Primary systemic vasculitic neuropathy
- Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis
  - Microscopic polyangiitis (MPA)
  - Eosinophilic granulomatous polyangiitis (EGPA, previously Churg-Strauss)
  - Granulomatosis with polyangiitis (GPA, previously Wegener’s granulomatosis)
- Polyarteritis nodosa (PAN)

When Would You Think About Systemic Vasculitis?

The key is involvement of other organ systems.

- Lungs
- Kidneys
- Joints
- GI tract
- Skin
- Eosinophilia
- Constitutional symptoms

ANCAs
  - Perinuclear ANCA react to myeloperoxidase (MPO)
  - Cytoplasmic ANCA react to proteinase-3 (PR3)
Polyarteritis Nodosa

- Medium vessel vasculitis
- No ANCA (differentiates from small vessel vasculitis)
- May be associated with hepatitis B
- Affects kidneys, skin, joints, GI tract, nerves
- Spares the lungs (differentiates from small vessel vasculitis)

Microscopic Polyangiitis and Granulomatous Polyangiitis

- Small vessel vasculitis
- Associated with ANCAs (GPA with PR3, MPA with MPO)
- No granulomas in MPA (unlike GPA, EGPA)
- Affects the ear, nose, throat (less in MPA)
- Tracheal/pulmonary involvement
- Renal involvement
- Skin- most common leukocytoclastic angiitis
- Eye involvement
Eosinophilic Granulomatosis with Polyangiitis

- Vasculitis of small and medium vessels
- Associated with MPO antibodies
- Phases of the disease
  - Prodromal
  - Eosinophilic
  - Vasculitic
- Ear and nose
- Respiratory involvement
- Skin - subcutaneous nodules
- Cardiovascular
- Renal (to a lesser extent than MPA and GPA)
- GI tract

Specific Forms of Vasculitic Neuropathies

- **Secondary systemic vasculitic neuropathy**
  - Rheumatoid arthritis
  - Sjögren’s syndrome
  - Systemic lupus erythematosus
  - Sarcoidosis
Specific Forms of Vasculitic Neuropathies

- **Non-systemic vasculitic neuropathy**
  - *No multiorgan involvement*
  - Weight loss and fever may be present
  - Mean age 59, women affected more often
  - Progressive asymmetric multifocal neurological deficits
  - 66-96% have pain


Specific Forms of Vasculitic Neuropathies

- **Specific forms of localized microvasculitis**
  - Diabetic and non-diabetic lumbosacral radiculoplexus neuropathy (DLRPN and LRPN)
    - Middle aged to older aged individuals with Type II DM
    - Frequent concomitant weight loss
    - Asymmetric, acute onset, hip/thigh>>foot/leg
    - Eventually bilateral
    - Pain → weakness
    - Autonomic symptoms
    - Upper extremity symptoms

Dividing Vasculitic Neuropathies by Histopathology

• **Nerve Large Arteriole**
  – Small arteries, large arterioles, smaller vessels
  – Pathologic changes are seen in epineural and perineural vessels (75-200 microns in diameter)

• **Microvasculitis**
  – Affects the smallest arterioles (<40 microns), microvessels, and venules

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**Nerve Large Arteriole**
- Primary systemic vasculitis
- Rheumatoid arthritis
- Hepatitis C
- Cryoglobulinemia
- HIV
- Paraneoplastic

**Microvasculitis**
- Sjögren’s
- NSVN
- DLRPN/LRPN
Clinical Features of Vasculitic Neuropathy

- Acute/subacute
- **Painful** sensory or sensorimotor deficits
- Mononeuropathy multiplex or asymmetric polyneuropathy
- Constitutional symptoms
  - Myalgias
  - Arthralgias
  - Weight loss
  - Abdominal pain
  - Night sweats

Evaluation of Vasculitic Neuropathies

**Labs**

- ANCAs
- CBC (eosinophils), CMP, urine, ESR, CRP, ANA, RF, ENA, complement, hepatitis B surface antigen, hepatitis C antibodies

**EMG**

- Asymmetrical or non-length dependent axonal neuropathy
- Occasional pseudo-conduction block
- Identify a nerve for biopsy
Biopsy in Vasculitic Neuropathies

- When is it indicated?
- **Nerve large arteriole vasculitis**
  - Epineurial and perineurial vessels
  - Fibrinoid necrosis of the tunica media/intima
- **Microvasculitis**
  - Smaller arterioles without internal elastic lamina, microvessels, and venules
  - Inflammation of the vessel wall with fragmentation and necrosis of the tunica media

Treatment of Systemic and Non-systemic Vasculitic Neuropathy

**Induction therapy**
- High dose corticosteroids
- Cyclophosphamide
- Methotrexate (milder disease)

**Refractory Disease**
- Rituximab
- IVIG
- PLEX

**Maintenance therapy**
- Cyclophosphamide
- Azathioprine
- Methotrexate
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Autoimmune Small Fiber Neuropathy
Definition
- Autoimmune sensory and autonomic neuropathy affecting the small unmyelinated and thinly myelinated nerves

Classic Presentation
- Length-dependent, non length-dependent, or generalized loss of thermal/pain sensation with associated neuropathic pain and autonomic dysfunction
Case #2: 57 Year-old Man with Diffuse Paresthesia

- 57 year old with no remarkable past medical history
- Acute onset paresthesia in feet
- Spread to hands, then lips, tongue, nose within weeks
- Refractory neuropathic pain
- No weakness
- Dry eyes and dry mouth

57 Year-old Man with Diffuse Paresthesia

Evaluation included:
- Normal nerve conduction studies and EMG
- Normal laboratory studies:
  - paraneoplastic, SPEP, ANA, ANCA, ESR, CRP, A1c, anti-SSA/SSB, angiotensin converting enzyme, hepatitis B and C, B6 and B12
Skin Biopsy

Normal

Abnormal

Lip Biopsy

http://library.med.utah.edu/WebPath/IMMHTML/IMM047.html
57 Year-old Man with Diffuse Paresthesia

Treatment

• 20 mg per day of prednisone for seronegative Sjögren’s syndrome

Differential Diagnosis of Small Fiber Neuropathy

Autoimmune
• Sarcoidosis
• Sjögren’s
• Paraneoplastic
• Celiac disease

Metabolic
• Glucose dysmetabolism
• Hypertriglyceridemia

Toxic
• Drugs
• ETOH

Infectious
• Hepatitis C
• Cryoglobulinemia
• HIV

Inherited
• Fabry
• Familial amyloidosis
• Hereditary sensory and autonomic neuropathy
• Sodium channel mutations

Other
• Amyloid
• Fibromyalgia
• Monoclonal gammopathy
Clinical Features of Autoimmune Small Fiber Neuropathy

- **Sarcoidosis**
  - Reported in up to 2/3 of sarcoidosis patients
  - Length-dependent and generalized presentations
- **Sjögren’s Syndrome**
  - Acute or slowly progressive
  - Length-dependent, generalized, or multifocal
  - Trigeminal nerve involvement

Other
- “Dysimmune”
  - acute onset generalized pain syndromes
  - childhood or adult onset
  - 89% had evidence of disordered autoimmunity on labs
- Celiac disease
- Paraneoplastic disease

Evaluation of Small Fiber Neuropathy

- **Skin Biopsy (Pathologic Gold Standard)**
  - Punch biopsy of the lateral distal leg (foot, distal thigh, proximal thigh)
  - Stained with pan-axonal marker protein gene product 9.5 (PGP 9.5)
  - Count intraepidermal nerve fiber density, sudomotor fibers, pilomotor fibers

- **Autonomic Testing**
  - Quantitative sudomotor axon reflex test (QSART)
    - Helpful for distal small fiber neuropathy
    - Thermoregulatory sweat testing

Treatment in Autoimmune Small Fiber Neuropathy

- Immunotherapy (corticosteroids, IVIg, other immunosuppressants)
- Symptomatic management
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Sensory Neuronopathy
Definition
• Neuropathy caused by damage to the dorsal root ganglia

Classic Presentation
• Early-onset ataxia
• Multifocal, asymmetric sensory deficits
Case #3: 76 Year-old with Progressive Ataxia

- Patient has a 1 year history of Sjögren’s syndrome (sicca symptoms, anti-SSA antibodies)
- Went from working 9 hour shifts to wheelchair-bound within 2 weeks.
- He denied “weakness” but could not walk because his legs were numb.
- He was diagnosed with Guillain-Barré syndrome and given IVIg.
- Received 4 more months of IVIg.
- Numbness then progressed.

76 Year-old with Progressive Ataxia

- Labs unremarkable: ESR, CRP, ANA, SPEP, ANCA, paraneoplastic, hepatitis B, C.
- MRI neural axis normal
- CSF remarkable for a protein of 89 mg/dL.
76 Year-old with Progressive Ataxia

Exam:

- Normal muscle bulk, tone, strength
- Decreased pinprick to the level of the waist
- Impaired proprioception to the level of the hips and to the level of the wrists
- Reflexes were absent in the legs, normal in the arms
- Severe gait ataxia, could not ambulate despite maximum assistance
76 Year-old with Progressive Ataxia

All of the following were attempted:
- Mycophenolate mofetil
- High dose corticosteroids
- Hydroxychloroquine
- IVIg

Anatomy of the Dorsal Root Ganglion

http://www.hcahealthcare.co.uk
Differential Diagnosis of the Acquired Sensory Neuronopathies

<table>
<thead>
<tr>
<th>Disease Association</th>
<th>Onset</th>
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<tbody>
<tr>
<td>Paraneoplastic</td>
<td>Subacute-Chronic</td>
</tr>
<tr>
<td>Small cell lung cancer, bronchial carcinoma, breast cancer, ovarian cancer, lymphoma, neuroendocrine tumours, sarcoma</td>
<td></td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Subacute-Chronic</td>
</tr>
<tr>
<td>Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, autoimmune hepatitis</td>
<td></td>
</tr>
<tr>
<td>Infection related</td>
<td>Subacute</td>
</tr>
<tr>
<td>HIV (also EBV, VZV, measles, HTLV-1)</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Subacute-Chronic</td>
</tr>
<tr>
<td>Platinum based chemotherapy (cisplatin, oxaliplatin, carboplatin), antibiotic toxicity has been suggested</td>
<td></td>
</tr>
<tr>
<td>Vitamin associated</td>
<td>Subacute-Chronic</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Chronic</td>
</tr>
<tr>
<td>Not Known</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features of Sensory Neuronopathies

- Upper limbs may be involved first/early
- Sensory loss involves the trunk, face, scalp, and eventually there is global loss of all sensory modalities
- Sensory ataxia
- Pseudoathetosis
- Autonomic dysfunction
- If overlap with other systems (brainstem, spinal cord, cerebellum-think paraneoplastic)
Evaluation of Sensory Neuronopathies

Labs
- Anti-Hu and anti-CV2/CRMP-5 antibodies (paraneoplastic)
- ANA, anti-SSA/SSB, ESR, CRP (autoimmune, Sjögren’s)
- CSF

EMG
- Severe, generalized, non-length-dependent sensory neuropathy
- Blink reflexes

Imaging
- Studies looking for malignancy
- MRI demonstrates increased T2-weighted signal in the posterior columns

Treatment of Sensory Neuronopathies

- Tumor treatment (paraneoplastic)
- Immunotherapy
- Symptomatic management
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Rheumatoid Arthritis-associated Polyneuropathy

- Nearly 60% of patients will have electrodiagnostic evidence of a neuropathy. 20% will be symptomatic.
- 2 primary groups of polyneuropathy included vasculitic and distal symmetric neuropathy.
  - Distal symmetric neuropathy is likely partially due to vasculitis.
  - Symptoms include pain, paresthesia, loss of sensation, and distal motor weakness.
- Demyelinating polyneuropathies are associated with anti-TNF alpha drugs

SLE-associated Polyneuropathy

- Polyneuropathy occurs in SLE 1-13% of the time.

- Distal sensory predominant polyneuropathy occurs most commonly (55% of the time)

- Corticosteroids, IVIG, rituximab, PLEX all used.


Sjögren’s Syndrome-associated Polyneuropathy

- Up to 22% of patients will have clinically evident polyneuropathy

- A pure sensory polyneuropathy constitutes 25-60% of all cases of polyneuropathy in Sjögren’s syndrome (small fiber, large fiber, or neuronopathy)

- Sensorimotor polyneuropathy may be associated with severe extraglandular disease

- Other forms of polyneuropathy
  - Demyelinating
  - Autonomic
  - Vasculitic
  - Polyradiculopathies

- Treatments include corticosteroids, IVlg, infliximab, rituximab, and TPE


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Trigeminal Neuropathy

Definition
- An isolated neuropathy of the trigeminal nerve

Classic Presentation
- Numbness in the skin or mucosal membranes in the distribution of the trigeminal nerves and neuropathic weakness of the muscles of mastication
Anatomy of the Trigeminal Nerve

Trigeminal Neuropathy versus Trigeminal Neuralgia

**Trigeminal Neuropathy**
- Numbness of the skin and mucosa
- Weakness of muscles of mastication

**Trigeminal Neuralgia**
- Brief attacks of lancinating pain
- No sensory impairment
- No motor impairment
Differential Diagnosis of Trigeminal Neuropathy

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Neoplastic</th>
<th>Vascular</th>
<th>Infectious</th>
<th>Trauma</th>
<th>Other</th>
<th>Idiopathic</th>
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</thead>
<tbody>
<tr>
<td>• Mixed connective tissue disease</td>
<td>• Carcinomatous meningitis</td>
<td>• Pontine ischemia or hemorrhage</td>
<td>• Leprosy</td>
<td>• Surgical</td>
<td>• Amyloid</td>
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<tr>
<td>• Sjögren's syndrome</td>
<td>• Intra or extracranial compression</td>
<td>• Vascular malformation</td>
<td>• Viruses</td>
<td>• Dental</td>
<td>• Pseudotumor cerebri</td>
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<td>• Progressive systemic scleroderma</td>
<td>• Perineural spread</td>
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<td>• Lyme</td>
<td>• Radiation</td>
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<tr>
<td>• Sarcoidosis</td>
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<td>• Syphilis</td>
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<tr>
<td>• Multiple sclerosis</td>
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<td></td>
<td>• Fungi</td>
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</tr>
</tbody>
</table>

Specific Forms of Trigeminal Neuropathy

- Undifferentiated and mixed connective tissue disease - most common
- Scleroderma- may be an isolated, early feature
- Sjögren’s syndrome
- Sarcoid- granulomatous disease of the trigeminal nerve
Clinical Features of Trigeminal Neuropathy

- Partial or complete sensory loss
- Occasional allodynia and hyperalgesia
- Corneal reflex affected
- Motor involvement is almost never a feature
- Neuropathic pain may be present

Evaluation of Trigeminal Neuropathies

- **Laboratory studies**
  - CBC, ESR, extractable nuclear antigen testing including SSA and SSB antibodies (salivary gland biopsy if necessary) RNP antibodies
- **Imaging**
  - MRI with and without contrast with attention to the skull base
- **Electrophysiological studies**
  - blink reflexes
Treatment of Trigeminal Neuropathies

- “Not an indication for immunosuppression”
- Symptomatic improvement with prednisone is rare
- Focus on symptomatic management of neuropathic pain
- Neurotrophic keratitis


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References #2