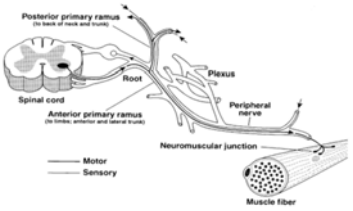
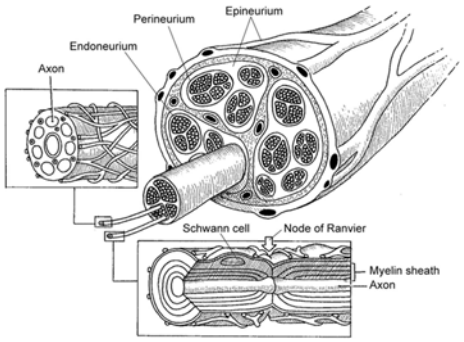
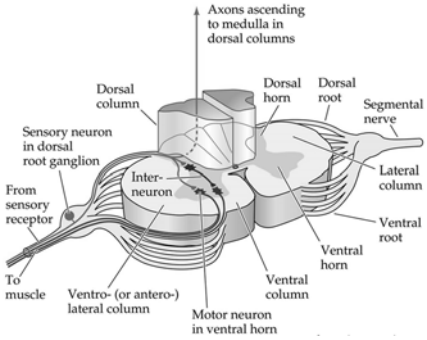
Disorders of the Peripheral Nervous System







Some observations we are making

- The audience is very smart and they know how to diagnose a neuropathy.
- There is a standard workup that all patients seem to get: B12, folate, RPR, TSH prior to them being referred to a neurologist.
- So the purpose of the talk will hopefully make the point of pitfalls in the diagnosis of neuropathy, how to think about diseases that mimic neuropathy and to expand your differential diagnosis and keep you interested with some challenging problems.

Case 1: Burning and tingling in the legs

- MD is an otherwise healthy 89 year old woman who complains of burning and tingling in her feet.
- She notices that this is worse when she walks a distance and it is worse at night when she lies flat on her back.

How do we interpret this history?

- How do we distinguish between neurogenic claudication vs. vascular claudication?
- How do we distinguish between the pain of a neuropathy vs. lumbosacral polyradiculopathy
- These two distinctions are important to make as it drives the workup in a different way
- Remember also that elderly patients may have multiple pathologies

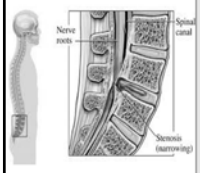


Table – Differentiating neurogenic and vascular claudication

Factors	Neurogenic	Vascular
Evaluation after walking	Increased weakness	Unchanged
Palliative factors	Bending over, sitting	Stopping
Provocative factors	Walking downhill Increased lordosis	Walking uphill Increased metabolic demand
Pulses	Present	Absent
"Shopping cart" sign	Present	Absent
van Gelderen bicycle test	No leg pain	Leg pain

Physical Examination

- She has excellent distal pulses and no risk factors for vascular disease
- She does have a known history for lumbar spinal stenosis
- There is no history of weight loss, night sweats and she has a normal diet.
- Physical examination of her legs demonstrates mild weakness of both EDB muscles.
- There is a distal length-dependent gradient of sensory hyperesthesia to light touch and pinprick to the level of the mid-calf.
- Joint position sense is impaired at the toes and there is mildly diminished vibration sense.

Workup

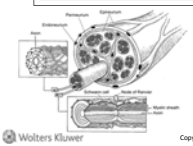
- Blood work demonstrates normal B12 and MMA levels
- Normal blood sugar and an % HgBA1C of 5.0
- SPEP: Monoclonal Gammopathy:
- Abnormal band in the Gamma Region identified as IgM Lambda (915mg/dl) which is 6% of total protein.
- There were no Bence Jones Proteins in the urine

MGUS: Monoclonal gammopathy of uncertain signficance

- Common in the general population and occur in 10% of patients with peripheral neuropathy.
- Initial workup is to look for Bence Jones Proteins in the urine, a skeletal survey and a consult with a hematologist.
- Annual SPEP as there is a transformation rate of 1% per year to a symptomatic plasma cell disorder.
- High risk factors for transformation include:
  - M protein of 15g/l or greater
  - Elevated free light chain ratio (ratio of kappa to lambda free light chains)
  - Non IgG protein

Hematological Disorders associated with paraproteinemias

Hematologic Disorder	Most Common Monoclonal Protein Type	Peripheral Neuropathy Phenotype	Electrodiagnostic Phenotype
Immunoglobulin M–monoclonal gammopathy of undetermined significance (IgM-MGUS)	IgM kappa	Distal large fiber sensory predominant neuropathy with sensory ataxia	Demyelinating with prolonged distal latencies
Waldenström macroglobulinemia	IgM kappa	Distal large fiber sensory predominant neuropathy with sensory ataxia	Axonal greater than demyelinating (with prolonged distal latencies)
Multiple myeloma	IgG more often than IgA	Length-dependent sensory, sensorimotor, or motor neuropathy	Axonal
Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome	IgG or IgA, lambda	Sensorimotor polyradiculoneuropathy (chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]-like)	Demyelinating
Immunoglobulin light chain (AL) amyloidosis	Lambda	Sensorimotor peripheral neuropathy with prominent autonomic involvement	Axonal



Paraproteinemic Neuropathies

Mauermann, Michelle L.
CONTINUUM: Lifelong Learning in Neurology. 20(5, Peripheral Nervous System Disorders):1307-1322, October 2014.

Overrepresentation of IgM paraprotein in patients with neuropathy

Paraprotein	Frequency of Heavy Chains in Patients With Monoclonal Gammopathy of Undetermined Significance	Frequency of Heavy Chains in Patients With Monoclonal Gammopathy of Undetermined Significance and Peripheral Neuropathy
Immunoglobulin M	15%	48%
Immunoglobulin G	73%	37%
Immunoglobulin A	12%	15%

[a] Reprinted with permission from Ramchandren S, Lewis RA, Curr Neurol Neurosci Rep.[6] © 2011, Springer Science and Business Media, LLC. link.springer.com/article/10.1007%2Fs11910-011-0237-4.
[b] Data from Gosselin S, et al, Ann Neurol.[10]
[c] Data from all patients with monoclonal gammopathy of undetermined significance evaluated at Mayo Clinic Rochester from 1961 to 1988.

Paraproteinemic Neuropathies

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Neuropathy Patterns and Type of Neuropathy Associated with multiple myeloma

Neuropathy Subtype	Characteristics
Multiple myeloma–associated neuropathy	
Multiple myeloma without amyloid	Distal sensory more common than motor neuropathy
	Rarely sensory ganglionopathy or motor polyradiculoneuropathy
Multiple myeloma with amyloid	Painful distal sensorimotor neuropathy with autonomic failure
Treatment emergent	
Bortezomib	Painful distal sensory neuropathy
Thalidomide	Painful distal sensory neuropathy
Vincristine	Distal sensorimotor neuropathy with autonomic involvement

Paraproteinemic Neuropathies

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Treatment options

- Symptomatic relief:
  - Anticonvulsants
  - Tricyclic antidepressants
  - SSRI's
- MGUS: First repeat SPEP at 6 months and then annually
  - If IGA and Ig M paraproteinemia (less motor weakness and if sensory ataxia) consider IVIG, plasmapheresis or even Rituximab (antiCD20 activity).
- Waldenstroms: per hematology, treatment is directed at bulky disease
- Myeloma: Neuropathy largely induced by treatment: Bortezomib (70%), Thalidomide (58-81%)
- POEMS Syndrome: Demyelinating polyneuropathy treated with plasma exchange, IVIG and radiation to the solitary plamacytoma

Case 2 presentation

- A 45-year-old teacher presented with a 6-month history of progressive bilateral foot, right thigh, and left face paresthesia.
- She denied loss of vision, diplopia, dysarthria, dysphagia, incontinence, limb weakness, or balance difficulty.
- She was recently diagnosed with hypertension and started on atenolol. She has a longstanding history of Type 1 diabetes (onset in her early 30's), well controlled with an A1C of 7.2.
- She was married with three children. She drank socially and did not smoke.
- She had a family history of Type 1 diabetes and ovarian cancer.

Case presentation

- Physical examination was remarkable for reduced sensation to pinprick in the V2 distribution of the left face and reduced sensation to pinprick in the right thigh and foot.
- The remainder of the neurologic examination was normal.
- MRI of the brain was normal.
- Electrodiagnostic testing of the legs, including bilateral sural and superficial peroneal responses, was normal. Blink reflex responses were normal.

So what would you do next?

Skin biopsy revealed normal right distal leg intraepidermal nerve fiber density and reduced right thigh intraepidermal nerve fiber density.

Is this just a small fiber neuropathy related to Diabetes ?

- Complete blood count and metabolic profile normal Hemoglobin A_{1c} 7.2
- Lyme disease, angiotensin-converting enzyme, anti-Hu antibodies, HIV, antinuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, double-stranded DNA, SS-A, SS-B, and gliadin IgA were normal.
- **Serum gliadin immunoglobulin (Ig) G and transglutaminase antibody levels were elevated.**
- **Duodenal biopsy revealed severe villous flattening, crypt hyperplasia, and intraepithelial lymphocytosis.**

Comment:

- This patient has a length-independent small fiber sensory polyneuropathy, which is confirmed by a decreased intraepidermal nerve fiber density.
- Lonstanding association of Type 1 diabetes and celiac disease
- A diagnosis of celiac disease (gluten-sensitive enteropathy) is suspected based upon the elevated gliadin IgG and transglutaminase antibodies and is confirmed by the duodenal biopsy findings. **Celiac neuropathy may occur in patients without gastrointestinal complaints.**

Case 3

- CS is an 18 year old college freshman with a history of Type 1 diabetes since the age of 5.
- Her diabetes is well controlled with an insulin pump and she is very vigilant.
- She reports worsening pain in her feet with tingling and numbness and is worried about diabetic neuropathy.

Pertinent Physical Examination of her feet

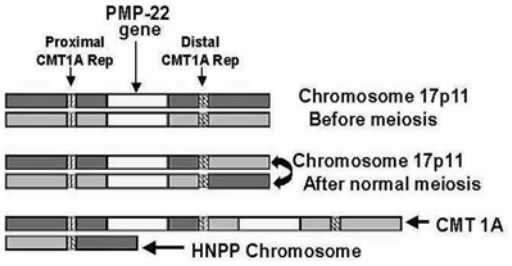
- She has high arches (pes cavus)
- There is mild weakness of foot and toe dorsiflexion.
- She is areflexic in her legs
- There is a stocking glove loss (to her mid-calf) involving pinprick, light touch, cold, joint position and vibration sense
- Her gait is high stepping and she has a positive Romberg.

What would you do next?

Single Gene Causes of CMT Hereditary Neuropathy

Type 1	Pathology	Mode of Inheritance	Proportion of CMT
CMT1	Abnormal myelin	AD	~50%
CMT2	Axonopathy	AD	~20-40%
Intermediate form	Combination of myelin and axonopathy	AD	Rare
CMT4	Either myelinopathy or axonopathy	AR	Rare
CMTX	Axonopathy with secondary myelin changes	X-linked	~10-20%

Segmental duplication in area containing PMP-22 gene on 1 chromosome 17
Occurs with abnormal alignment during meiotic crossing over Leads to total of 3 copies of PMP-22 gene



Treatment options for neuropathy: Big discussion

- General principles
  - Try to treat the underlying cause (30% of the time we will find a treatable cause)
  - If medication related, will have to stop the medicine if possible (difficult decision with chemotherapy).
  - Stop all alcohol
  - Avoid narcotics
  - Multimodal therapy: Tricyclics, Anticonvulsants, SNRI's etc
  - Symptomatic treatment
  - Systemic treatment for demyelinating neuropathies: plasmapheresis, IVIG
- Orthopedic supports: AFO's, podiatry, foot orthotics, aqua therapy

Case 4: Sudden ascending weakness and rash

- WR is a 67 year old man with a history of coronary artery disease who underwent a cardiac catheterization at a hospital in New Hampshire.
- Approximately 5 months later, he felt ill and complained of a rash that developed over his legs.
- He quickly developed weakness in his legs and was unable to support his weight.
- He was diagnosed with Hepatitis C, which was contracted by contaminated needles during his cardiac catheterization procedure. He had been tested for Hep C following a blood transfusion 6 months prior to the cardiac catheterization.

Additional history:

- He noted weakness in his legs while walking his dog.
- He had difficulty getting up out of a chair.
- He fell many times.
- He has trouble with his memory.
- He also has trouble now holding a pen.
- Things got worse, but the rash on the legs together with the weakness prompted him to be transferred from the outside hospital.

Neurological Examination

- There was weakness in the intrinsic muscles of his hands
- There was marked weakness of his iliospoas, hamstrings and quadriceps bilaterally (4/5).
- There is severe weakness of both EHL muscles and he has bilateral foot drop and flail ankles.
- There is asymmetric median sensory loss distribution to pinprick in the hands and he has stepwise loss to pinprick in the legs. He has absent joint position sense and vibration sense.
- There are no reflexes attainable in his legs.

How do we put the examination together with the rash?

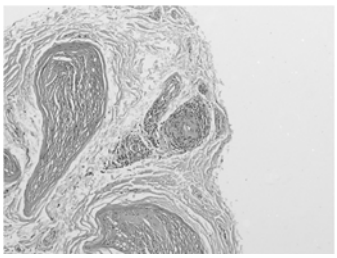
Localization of his neurological findings

- Global weakness, all muscles involved
- Areflexia
- "Step wise sensory loss"
- Multiple nerves: Median, common peroneal

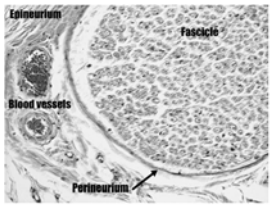
  - MONONEURITIS MULTIPLEX

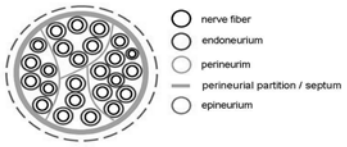
Neuropathology

Small vessel vasculitis involving vessels of the epineurium with fibrinoid necrosis and apoptotic debris within the vessel wall



Vasculitic Neuropathy: Mechanism of Injury





Vasculitic Neuropathy: Clinical Presentation

- Acute or subacute symptom onset
- Chief Concerns:
  - Pain
    - Deep aching pain = poorly localized (attrib to acute ischemia)
    - Cutaneous burning pain hours-days later
  - Painful sensory/sensorimotor neuropathy
    - Mononeuritis multiplex (sometimes confluent) and asymmetric polyneuropathy = most common neurological manifestations
    - Initial symptoms generally in lower limbs, feet
- Associated Symptoms:
  - migratory arthralgias, myalgias, respiratory symptoms, weight loss, abdominal pain
  - Autonomic dysfunction Uncommon

Vasculitic Neuropathy: Investigation

- CSF
  - Most helpful to evaluate for "mimickers"
- SERUM
  - CBC, chem-7
  - SPEP
  - Hep B + C, HIV, lyme
  - Cryoglobulins and test rheumatoid factor which binds to an epitope
  - +/- complement levels (if suspect cryo or SLE)
  - ESR, CRP, ANA, RF, ACE
  - ANCA

Final Diagnosis

- **Cryoglobulinemic Vasculitis secondary to acute Hepatitis C**