DIABETIC NEUROPATHIES

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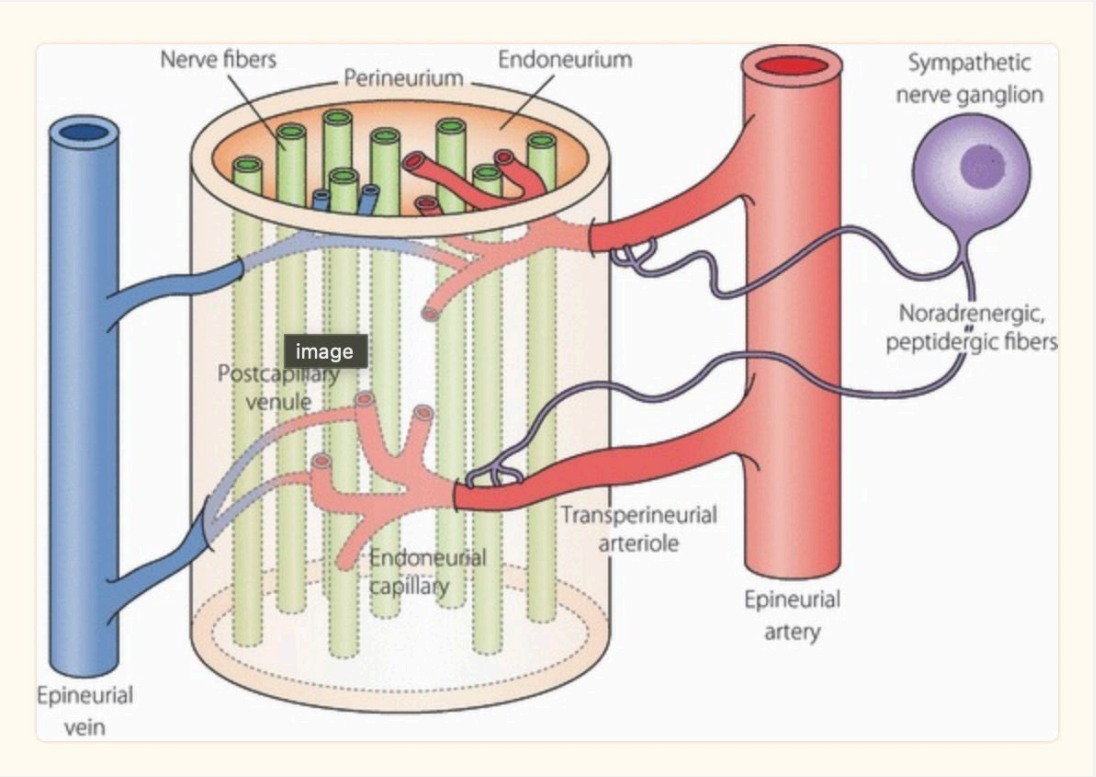
OVERVIEW

- Diabetes affects about 10% of Americans
- Approximately 50% will develop neuropathy
- Neuropathic pain is seen in about 25% of cases

PATHOPHYSIOLOGY

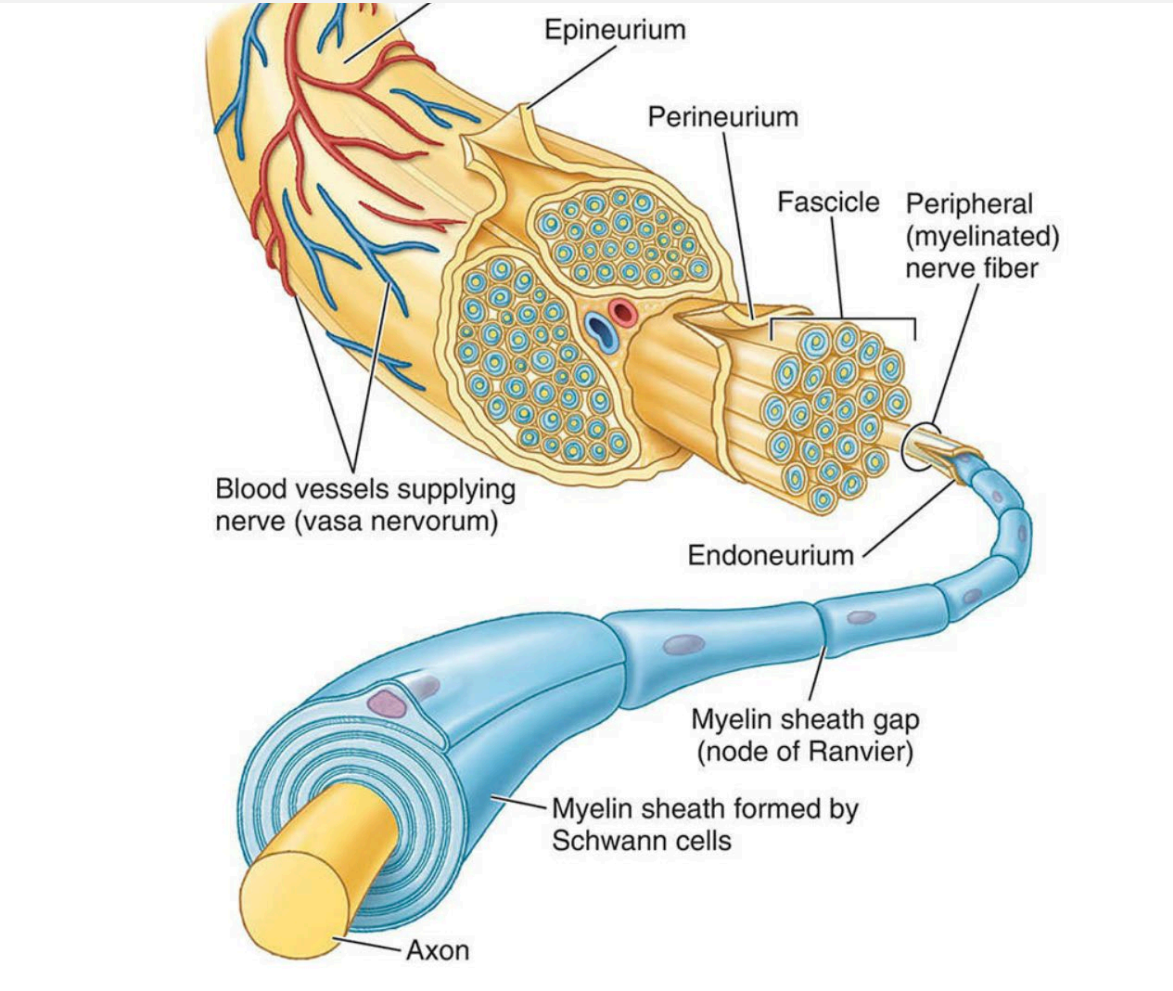
NERVE REPAIR ⟷ NERVE DAMAGE

- Distal nerves are more vulnerable:
  - Oxidative stress to mitochondria in the dorsal root ganlgia
  - Glycosylation end products
  - Neurovascular impairment



PATHOLOGY

It is a distal dying back axonopathy, primarily affecting sensory nerves



PHYSICAL EXAMINATION

1. Cranial nerves
   - Eye and facial movements
2. Motor:
   - Focus on toe flexors, toe extensors, and intrinsic hand muscles
3. Sensory:
   - Light touch, pinprick, **vibration (128 Hz), proprioception**
   - Two point discrimination
   - **10 gram monfilament**
4. Reflexes:
   - **Ankle jerk** and patella
5. Skin:
   - Mottling, pallor, erythema, **painless foot ulcers**

Clinically diagnostic exam findings

MICHIGAN NEUROPATHY SCREENING INSTRUMENT

16.4.5. *Monofilament Test*

1.For this examination, it is important to support the patient's foot (i.e., allow the

2.sole of the foot to rest on a flat, warm surface).

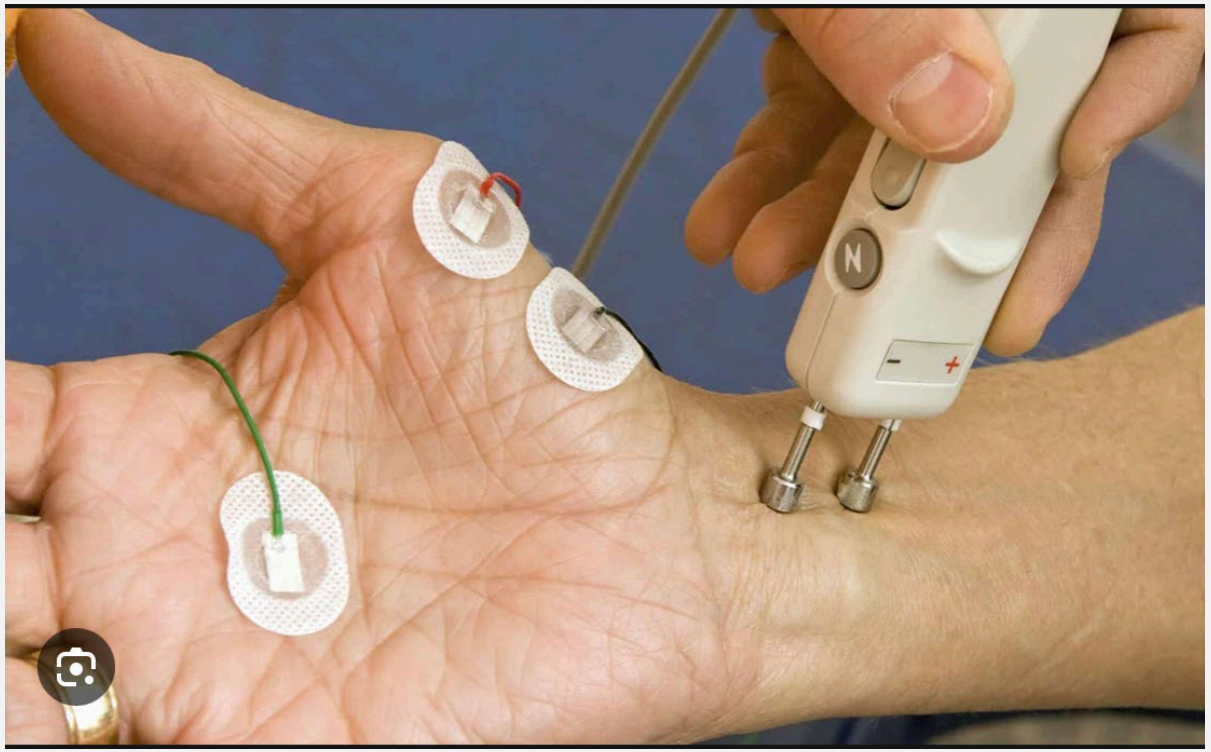
3.Prestress the filament by applying it to the dorsum of your first finger 4-6 times.

4.Ask the patient to close his/her eyes. Apply the filament perpendicularly and briefly (<1 second) with an even pressure to the dorsum of the great toe midway between the nail fold and the DIP joint. Do not hold the toe directly. When the filament bends, the force of 10 grams has been applied.

5.Ask the patient to respond "yes" if he/she feels the filament. Recall that eight correct responses out of 10 applications is considered normal: one to seven correct responses indicates reduced sensation, and no correct answers translates into absent sensation.

TESTING
NOT ALWAYS NEEDED

- Labs: depend on the phenotype
- NCS/EMG
  - Primarily axonal, with a touch of demyelination
- Skin biopsy
- Autonomic testing
  - orthostatic blood pressure measurements
  - Quantitative sudomotor axon reflex test



TYPES OF DIABETIC NEUROPATHY

1. **Distal symmetric polyneuropathy**
2. **Small fiber neuropathy**
3. Acute severe distal sensory polyneuropathy
4. **Autonomic neuropathy**
5. **Diabetic neuropathic cachexia**
6. Hypoglycemic neuropathy
7. **Treatment induced neuropathy**
8. Polyradiculopathy
9. **Diabetic radiculoplexus neuropathy**
10. **Mononeuropathies**
11. **Cranial neuropathies**

DISTAL SYMMETRIC POLYNEUROPATHY

- Classic small fiber symptoms include burning pain, shooting pains, tingling, sympathetic vasomotor changes (pallor, rubor, cyanosis, mottling)
- Large fiber symptoms include numbness, tingling, impaired balance, and "weakness."
- Sural response

SMALL FIBER NEUROPATHY

- Classic small fiber symptoms include burning pain, shooting pains, tingling, sympathetic vasomotor changes (pallor, rubor, cyanosis, mottling)
- Some autonomic symptoms can be seen
- **Nerve conduction studies will be normal**
- Reduced intraepidermal nerve fiber density via skin biopsy
- Reduced QSART
- Screen for alcohol use

AUTONOMIC NEUROPATHY

- Present in about 20% of diabetics with associated increased mortality
- Usually an advanced symptom
- Symptoms:
  1. Cardiovascular: resting fixed tachycardia (vagal), orthostatic hypotension, exercise intolerance, perioperative complications
  2. Gastrointestinal: early satiety, constipation, dry mouth
  3. Skin: abnormal sweat patterns, dry skin, temperature changes
  4. Genitourinary: erectile dysfunction
  5. Eyes: reduced night vision, dry eyes

DIABETIC AMYOTROPHY

- Usually type 2 diabetics
- Can occur despite good control
- Disease mimics include orthopedic pain, lumbosacral polyradiculopathies, and vasculitic neuropathy
- Walker or wheelchair

- Weeks to months of progressive severe asymmetric pain, numbness, and proximal greater than distal weakness with atrophy
- Symptoms can migrate to the opposite leg and distal hands
- Weight loss
- Progression over 1-2 years is common

- **IV methylprednisolone?**

DIABETIC NEUROPATHIC CACHEXIA

- More common in older men
- Severe neuropathic pain, distal weakness, and numbness
- Weight loss
- Partially reversible with aggressive management of diabetes
- Pain can be refractory

TREATMENT INDUCED NEUROPATHY

- Associated with rapid correction of poorly controlled diabetes, typically greater than 2-3% over 3 months
- Possibly related to sudden relative glucose deprivation in nerves and AV shunts causing endoneural ischemia
- Management is controversial
  - Permissive hyperglycemia?
  - No changes?
- In one study, patients who maintained stable control had near-complete functional recovery over several years. Patients with poor control worsened.

MONONEUROPATHY

- Diabetic oculomotor palsy is the most common cranial neuropathy
- Compressive neuropathies are far more common
  - Carpal tunnel syndrome prevalence is 14% in diabetes (versus 3% in control)
  - In diabetics with DSPN, CTS prevalence is 30%

DOES DSPN GET BETTER?

- Interventions are intended to halt progression but do not reverse in most cases
- A few small clinical trials showed slight improvements in electrodiagnostic with adequate glycemic control
- Some symptoms like pain can definitely improve
- Entrapment neuropathies can definitely be treated

PREDIABETES AND SMALL FIBER NEUROPATHY

- Publication: *Prediabetes, diabetes, metabolic syndrome, and small fiber neuropathy* from Muscle and Nerve.

- Conclusion*:* **"**DM, but not PD alone, is associated with SFN.**"**

- **The controversy continues!**

TREATMENT

- Impaired glucose tolerance is reversible!
  - Diabetes Prevention Program study: 3244 patients with impaired glucose tolerance randomized to placebo, metformin, or intensive diet and exercise. Of the placebo group, 30% developed diabetes n 3 years but 25% normalized. Lifestyle intervention reduced diabetic incidence by 58% (NNT 7), metformin by 31% (NNT 14), compared to placebo
- Lifestyle, lifestyle, lifestyle

TREATMENT IDEAS

- SNRI: my favorite
  - Duloxetine (20 - 120 mg daily) or Venlafaxine (37.5 - 225 mg daily)
- Gabapentin (300-3600 mg daily)
- Pregabalin (75 – 600 mg daily)
- Tricyclic antidepressants:
  - Nortriptyline (25 - 100 mg daily) or amitriptyline (25 - 100 mg daily)
- Alternatives:
  - Capsaicin cream (0.075% topically four time daily), 5% lidocaine patches (12 hours per 24 hours, lidocaine cream (4%)
- TENS unit
- Alpha lipoic acid 600 mg daily

UNIQUE TREATMENT

- Diabetic amyotrophy:
  - 500 mg IVMP qweekly for 8-12 weeks
- Autonomic neuropathy
  - Start by reviewing medications
  - Consider non-pharmacological strategies like compression stockings (above knee), isometric exercises, stooping or squatting, crossing legs, raising the head of the bed, or drinking 500 cc of water prior to exertion
  - Salt tablets, midodrine, fludrocortisone, pyridostigmine

WHAT SHOULD YOU DO?

1. For classic DSPN and small fiber neuropathy:
   - Per ADA guidelines, you can make a clinical diagnosis
2. For atypical DSPN (rapid progression, weakness on exam, unexplained falls, bowel or bladder dysfunction)
   - Refer to neurology with NCS/EMG
3. For monomelic symptoms
   - Refer patients for nerve conduction studies
4. For upper extremity symptoms:
   - Refer patients for nerve conduction studies
5. For everything else:
   - Refer to neurology