DIABETIC NEUROPATHIES

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Disclosures-Pfizer
(Familial Amyloid Polyneuropathy)

Off label use of medications will be discussed
Peripheral Neuropathy

- Common problem
  - non-traumatic peripheral neuropathy
  - prevalence of 2.4% in population
  - prevalence of 8% over the age of 55
Peripheral Neuropathy

• Most common cause (in developed nations) is diabetic mellitus

• Prevalence of diabetic peripheral neuropathy expected to rise in the U.S.
Diabetes affects:
25.8 million people of all ages
8.3 percent of the U.S. population

DIAGNOSED
18.8 million people

UNDIAGNOSED
7.0 million people
Complications of Diabetes

**Neuropathy**

60-70%

Polyneuropathy, Autonomic Neuropathy, CTS, etc

Major contributor of amputations

**Lower Limb Amputations**

>60% of non-traumatic amputations

65,700 amputations from 2006
Prevalence of Diabetic Neuropathies

Prevalence of Neuropathy in the Rochester Diabetic Neuropathy Study, 1986

Prevalence figures are age- and sex-adjusted to the Rochester, MN population.

(Dyck PJ et al. Neurology 1993; 43(4):817-24.)
## Diabetic Neuropathies

(Boulton et al, 2005)

<table>
<thead>
<tr>
<th>Classification of diabetic neuropathy</th>
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<tbody>
<tr>
<td>Generalized symmetric polyneuropathies</td>
</tr>
<tr>
<td>• Acute sensory</td>
</tr>
<tr>
<td>• Chronic sensorimotor</td>
</tr>
<tr>
<td>• Autonomic</td>
</tr>
<tr>
<td>Focal and multifocal neuropathies</td>
</tr>
<tr>
<td>• Cranial</td>
</tr>
<tr>
<td>• Truncal</td>
</tr>
<tr>
<td>• Focal limb</td>
</tr>
<tr>
<td>• Proximal motor (amyotrophy)</td>
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<tr>
<td>• Coexisting CIDP</td>
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</tbody>
</table>

Adapted from Thomas (4). Note: Clinicians should be alert for treatable neuropathies (CIDP, monoclonal gammopathy, vitamin B<sub>12</sub> deficiency, etc.) occurring in patients with diabetes.
Overview - Diabetic Neuropathies

- Diabetic Polyneuropathy and Autonomic Neuropathy
  - Symptoms
  - Signs
  - Complications
  - Evaluations
  - Management
  - Treatment
Diabetic Neuropathy

Risk Factors
- High blood sugars
- Coronary artery disease
- Increased triglyceride levels
- Body mass index > 24
- Smoking
- High blood pressure

Pathophysiology
- HYPERGLYCEMIA
- Cardiovascular risk factors
- Lipid alterations
- Increased polyol flux
- Accumulation of advanced glycation end products
- Oxidative stress

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Diabetic Polyneuropathy (DPN)

Definition of DPN for clinical practice: “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes”.
Diabetic Polyneuropathy

Diagnosis cannot be made without a careful clinical examination of the lower limbs, as absence of symptoms should never be assumed to indicate an absence of signs.
Symptoms of DPN

- Tingling
- Burning pain
- Electrical or stabbing sensations
- Hypersensitivity
- Deep aching pain
- Weakness
- Imbalance
- Fatigue
- Falls
- Worse in feet
- Worse at night
Signs of DPN

• Distal sensory loss:
  – vibration
  – pinprick
  – temperature
  – absent or reduced ankle reflexes

• Distal weakness
  – Toes
  – Fingers
Complications of DPN

- Risk of injury due to lack of sensation
- Charcot joints
- Foot ulcers
- Amputations
DPN

• Absence of retinopathy and nephropathy

• Exclusion of other causes

• Other causes of polyneuropathy
  - Hypothyroid, Vitamin B12 deficiency, hepatitis C, HIV, medications
Differential Diagnosis in Diabetic Polyneuropathy

- Small fiber neuropathy
- Cervical myelopathy
- Lumbosacral radiculopathy
- Plantar fasciitis
- Osteoarthritis
Diagnosis

• EMG
• Quantitative Sensory Testing
• Skin biopsy
• Autonomic Testing
Electromyography (EMG)

- Two part test:
  - Nerve conduction studies
  - Needle electromyography

- Establish diagnosis of polyneuropathy
- Distinguish demyelinating from axonal
- Differentiate radiculopathy, plexopathy

- Normal in small fiber and autonomic neuropathy
Quantitative Sensory Studies

• Quantitative outcomes in research
• Small fiber neuropathy

• Computer assisted sensory testing
  • Vibration
  • Cold
  • Heat-pain
Fixed cryosections of skin biopsy specimens from the distal part of the leg of a healthy subject (A) and patient 4 (B), who has an abnormally low epidermal nerve fiber density (immunoperoxidase stain of protein gene product 9.5 [a panaxonal marker], original magnification x400)

Management

- Control of blood sugar levels
  - More frequent monitoring
  - Change in medication
  - HbA1c < 7%

- Avoidance of extreme glucose fluctuations
  - Hyperglycemia
  - Hypoglycemia
  - Nutritional education
Diabetic Polyneuropathy: Management

• In general, every percentage point drop in A1C (e.g. from 8.0 to 7.0%) can reduce the risk of microvascular complications—eye, kidney, and nerve diseases—by 40%.
Management

Care of feet

- Inspect feet daily (mirror)
- Keep feet clean and moisturized
- Foot care with podiatrist
- Molded shoes
- Avoid walking barefoot
- Checking temperatures of water/sand
Management

Rehabilitation for weakness and balance

• Physical therapy
  • maintain strength and flexibility
  • Balance,
  • Fall avoidance
  • cane, braces, walker, motorized vehicle

• Occupational Therapy
  • Activities of daily living
Treatment

• Analgesics (ASA, acetaminophen, NSAIDS)
• Antidepressants medications
• Anesthetic medications
• Narcotics
• Antioxidant medications (ALA 600 mg)
<table>
<thead>
<tr>
<th>Level</th>
<th>Recommended drug and dose</th>
<th>Not recommended</th>
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<tbody>
<tr>
<td>Level A</td>
<td>Pregabalin, 300–600 mg/day</td>
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<tr>
<td></td>
<td>Gabapentin, 900–3600 mg/day</td>
<td>Oxcarbazepine</td>
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<tr>
<td></td>
<td>Sodium valproate, 500–1200 mg/d</td>
<td>Lamotrigine</td>
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<tr>
<td></td>
<td>Venlafaxine, 75–225 mg/day</td>
<td>Lacosamide</td>
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<td></td>
<td>Duloxetine, 60–120 mg/day</td>
<td>Clonidine</td>
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<td></td>
<td>Amitriptyline, 25–100 mg/day</td>
<td>Pentoxifylline</td>
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<tr>
<td>Level B</td>
<td>Dextromethorphan, 400 mg/day</td>
<td>Mexiletine</td>
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<tr>
<td></td>
<td>Morphine sulfate, titrated to 120 mg/day</td>
<td>Magnetic field treatment</td>
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<tr>
<td></td>
<td>Tramadol, 210 mg/day</td>
<td>Low-intensity laser therapy</td>
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<tr>
<td></td>
<td>Oxycodone, mean 37 mg/day, max. 120 mg/day</td>
<td>Reiki therapy</td>
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<tr>
<td></td>
<td>Capsaicin, 0.075% four times per day</td>
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<tr>
<td></td>
<td>Isosorbide dinitrate spray</td>
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<td>Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks</td>
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Treatment

• Prevention of secondary issues
  – Osteoporosis
  – Depression
  – Social isolation
Diabetic Autonomic Neuropathy
Autonomic Symptoms

• Orthostatic (lightheadedness)
• Visual (blurred vision, glare, reduced night vision)
• Secretomotor (dry eyes and dry mouth)
• Gastrointestinal (satiety, diarrhea, constipation)
• Urogenital (bladder dysfunction, ED)
• Sudomotor (decreased/increased)
• Vasomotor (cold extremities)
Postural hypotension

- Fall in SBP > 20 mm Hg
- Lightheadedness, dizziness, weakness, fatigue, cognitive changes, syncope
- May be exacerbated by insulin
- Worse postprandial
- Exacerbated by anemia
Diabetic Autonomic Neuropathy (DAN)

- Cardiovascular symptoms
- Unexplained tachycardia
- Orthostatic hypotension
- Poor exercise intolerance

- 2.5-50% prevalence
DAN

• Predictors:
  – Duration of diabetes
  – Glycemic control
  – Polyneuropathy/retinopathy/nephropathy
DAN

• Associated with:
  – Intraoperative cardiovascular instability
  – Silent myocardial infarction and ischemia
  – Increased mortality
Testing for DAN

- Screening at diagnosis of type 2 DM
- 5 years after diagnosis of type 1 DM
- Severe DAN-worse prognosis

Autonomic Testing

• Battery of non-invasive tests
  • Sympathetic cholinergic (sudomotor)
  • Parasympathetic cardiovagal
  • Sympathetic adrenergic
Autonomic Testing

- Quantitative Sudomotor Axon Reflex Test
- Heart rate response to deep breathing
- Valsalva Maneuver (not retinopathy)
- Tilt Table
Quantitative Sudomotor Axon Reflex Test

(Low et al. Ann Neurol 1983;14:573)
Heart rate response to deep breathing

(Wang and Kaufmann. Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders. TE Bertorini ed.)
Valsalva Maneuver

Tilt Table

(Wang and Kaufmann. Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders. TE Bertorini ed.)
Management

- Cardiac Evaluation
- Review medications (adverse effects)
- Avoid dehydration
- Avoid extreme temperatures
Management

• Orthostatic hypotension
  – Sit on edge of bed/dorsiflex feet
  – Fluids (8 cups/day)
  – Salt
  – 6 small meals
  – Cross legs
  – Compression stockings/Abdominal binder
  – Walker/wheelchair
Treatment

• Fludrocortisone
  – Mineralocorticoid
  – 0.1-0.4 mg/day
  – Monitor potassium
  – Supine hypertension
  – Edema
Treatment

• **Midodrine**
  – Alpha adrenoreceptor agonist
  – 10 mg three times daily
  – Up to every 4 hours
  – Avoid after 6 pm
  – Goosebumps (piloerection)
Questions