Neurologic Complications of Diabetes
Polyneuropathy and More

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Background

Neuropathy: Any damage to the peripheral nervous system

- Affects 2% of all people, 15% of those age 40 and over
- Diabetes is the most common underlying etiology
- 50% of diabetics have neuropathy by 25 years after onset
- 10%–100% have subclinical peripheral polyneuropathy, depending on study
- Type 1 appears to have higher risk in adolescents — 26% vs. 8% of Type 2
- Can appear in prediabetes as well
Poll

How many of your patients have diabetic neuropathy?

A. 0%
B. 1%–25%
C. 26%–50%
D. 51%–75%
E. 76%–99%
F. 100%
Pathogenesis

- Multiple pathways to damage in a cell:
  - Osmotic stress, reactive oxygen species, glycolysis overload, AGE-induced inflammation, and loss of nerve repair factors like nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, insulin-like growth factor, and VEGF. Insulin (missing in T1DM) is also neurotrophic factor.
Pathogenesis (2)

Pathogenesis (3)

A spectrum of impact accounts for the variety of diseases seen
Classification of Diabetic Neuropathies

Symmetric Polyneuropathies:
- Progressive:
  - Length-dependent polyneuropathy
  - Autonomic neuropathy
- Episodic:
  - Diabetic neuropathic cachexia
  - Treatment-induced diabetic neuropathy

Asymmetric, Focal, and Multifocal neuropathies:
- Diabetic radiculoplexopathy (diabetic amyotrophy; proximal diabetic neuropathy)
- Thoracic radiculopathy
- Cranial neuropathies
- Mononeuropathy
Classification of Diabetic Neuropathies (2)

Length-dependent Polyneuropathy

- **Sensory:**
  - Stocking-glove pattern
  - Positive: burning, tingling, extra-sensitive
  - Negative: numbness
  - Worse at rest, nocturnal exacerbation
  - Imbalance: 2–3 times fall risk
- **Motor:**
  - Mild or absent
  - Foot muscle atrophy
  - Not proximal
- Absent or reduced tendon reflexes
Poll: Length-dependent Neuropathy

How many of your patients have length-dependent neuropathy?

A. 0%
B. 1%–25%
C. 26%–50%
D. 51%–75%
E. 76%–99%
F. 100%
Length-dependent Polyneuropathy (2)

• Exclude other causes

Length-dependent polyneuropathy
Check vitamin B12 and metabolites with metformin use and decline


Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care 2010; 33 (1): 156Y161
Length-dependent polyneuropathy
Intraepidermal nerve fiber density testing

**IENF Density Mean (fibers/mm)**

<table>
<thead>
<tr>
<th></th>
<th>Diabetic</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>5.4(±6.7)</td>
<td>15.7(±17.8)</td>
</tr>
</tbody>
</table>

Images of skin and nerve fibers are also shown.
Length-dependent Polyneuropathy
Glycemic Control

- **Glycemic control**
- Pain control
- Nerve therapy

Length-dependent Polyneuropathy
Pain Control

- Glycemic control
- Pain control
- Nerve therapy


Table 3: Comparison of EFNS and AAN guidelines for pharmacological treatment of diabetic neuropathic pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>EFNS</th>
<th>AAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin (300-600 mg a day)</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>A/B*</td>
<td>B†</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>A/B*</td>
<td>B†</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>A/B*</td>
<td>B†</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>A/B*</td>
<td>B</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>A</td>
<td>B (amitriptyline)</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitor</td>
<td>A</td>
<td>B (venlafaxine, duloxetine)</td>
</tr>
<tr>
<td>Opioids (oxycodone)</td>
<td>A</td>
<td>B (morphine, oxycodone)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Topical capsaicin</td>
<td>A/B*</td>
<td>B</td>
</tr>
<tr>
<td>Isosorbide spray</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>ABT-594</td>
<td>A</td>
<td>--</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>B</td>
<td>--</td>
</tr>
<tr>
<td>Levodopa</td>
<td>B</td>
<td>--</td>
</tr>
<tr>
<td>Lidocaine patch</td>
<td>--</td>
<td>C</td>
</tr>
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EFNS=European Federation of Neurological Societies task force. AAN=American Academy of Neurology. A=established as effective. B=probably effective. C=possibly effective. *Drug classed as ineffective or with discrepant results. †Drug not recommended.
Length-dependent Polyneuropathy
Pain Control (cont.)

- Glycemic control
- Pain control
- Nerve therapy


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<tr>
<th></th>
<th>EFNS*2</th>
<th>AAN*4</th>
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</thead>
<tbody>
<tr>
<td>Pregabalin (300–600 mg a day)</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>A</td>
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Table 3: Comparison of EFNS and AAN guidelines for pharmacological treatment of diabetic neuropathic pain
Poll: Medications

Which pain medications do you use most?
A. Gabapentin
B. Pregabalin
C. TCAs (amitriptyline, nortriptyline, etc.)
D. SNRIs (duloxetine, venlafaxine)
E. Topicals (capsaicin, lidocaine, etc.)
F. Combination therapy
Length-dependent Polyneuropathy
Nerve Therapy

- Glycemic control
- Pain control
- Nerve therapy

**Viromed – VM202:**
- Phase III trial, with estimated completion 6/2019.
- Double-blind, randomized, placebo-controlled, multicenter study
- Hepatocyte growth factor with potential neurotrophic effect

**Vertex – VX-150:**
- 3rd Phase II trial was successful 12/2018.
- NaV1.8 sodium channel inhibitor
- Found in dorsal root ganglion and unmyelinated C-fibers for nociception
Autonomic Neuropathy

**Sympathetic**
“Fight or flight”
- Activating
- Increases heart rate
- Dilates pupil
- Inhibits GI activity
- Closes sphincters
- Increases sweating
- Diverts blood from skin and GI tract to skeletal muscles

**Parasympathetic**
“Rest and digest”
- Relaxing
- Lowers heart rate
- Constricts pupil
- Promotes digestion, GI peristalsis
- Empties bladder
- Relaxes sphincters
- Mediates genital erection
# Autonomic Neuropathy (2)

<table>
<thead>
<tr>
<th>Category</th>
<th>Symptoms/Signs</th>
<th>Diagnostic Tests</th>
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</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Orthostasis</td>
<td>Heart rate variation to deep breathing/Valsalva maneuver</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
<td>Blood pressure variability to grip, standing, tilt</td>
</tr>
<tr>
<td></td>
<td>Silent ischemia</td>
<td>PET cardiac scintigraphy</td>
</tr>
<tr>
<td></td>
<td>Reduced exercise tolerance</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>Gastric emptying study</td>
</tr>
<tr>
<td></td>
<td>Early satiety</td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Constipation/diarrhea</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Erectile dysfunction</td>
<td>Nocturnal penile plethysmography</td>
</tr>
<tr>
<td></td>
<td>Retrograde ejaculation</td>
<td>Postvoid residual</td>
</tr>
<tr>
<td></td>
<td>Reduced vaginal lubrication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurogenic bladder</td>
<td></td>
</tr>
<tr>
<td>Cutaneous/sudomotor</td>
<td>Anhidrosis</td>
<td>Quantitative sudomotor axon reflex testing</td>
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<tr>
<td></td>
<td>Dry skin</td>
<td>Sympathetic skin response</td>
</tr>
<tr>
<td></td>
<td>Heat intolerance</td>
<td>Thermoregulatory sweat testing</td>
</tr>
<tr>
<td>Pupillary</td>
<td>Argyll Robertson pupil</td>
<td></td>
</tr>
<tr>
<td>Central, integrative</td>
<td>Hypoglycemic unawareness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reduced hypoxia-induced ventilatory drive</td>
<td></td>
</tr>
</tbody>
</table>

Smith AG, Singleton JR. Neurology Continuum 2012; 18 (1): 60–84
Poll: Autonomic Neuropathy

How many of your patients have autonomic neuropathy?
A. 0%
B. 1%–25%
C. 26%–50%
D. 51%–75%
E. 76%–99%
F. 100%
Autonomic Neuropathy (3)

- Clinically seen in 5%–35% of diabetics
- Vagus nerve often affected first
- Subclinical autonomic dysfunction is very common
- Mild dysfunction in up to 75% of those with length-dependent polyneuropathy
- Marker of adverse cerebrovascular, cardiovascular, and renal outcomes
Autonomic Neuropathy
Five-year mortality rate is 2–5 times higher

Autonomic Neuropathy (4)

Cardiac

• Heart rate changes
  • Impaired HR variability
  • Resting tachycardia, postural tachycardia, fixed bradycardia

• Blood pressure changes
  • Orthostatic hypotension
  • Postprandial hypotension
  • Nocturnal hypertension

• Limited exercise tolerance
Autonomic Neuropathy (5)

**Figure 3-7** Marked blunting of heart rate response to deep breathing is shown in a 25-year-old woman with type 1 diabetes and dysautonomia compared to normal response in an age-matched control. Beat-to-beat RR interval is shown.

BPM = beats per minute.

Autonomic Neuropathy
Gastrointestinal

Owyang, C. “Phenotypic Switching in Diabetic Gastroparesis: Mechanism Directs Therapy.” *Gastroenterology*; 2011; 141 (4); 1134–1137
## Autonomic Neuropathy
### Gastrointestinal (cont.)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mechanisms</th>
<th>Therapeutic Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early satiety and postprandial fullness</td>
<td>Defective accommodation</td>
<td>NO donors</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Gastroparesis secondary to enteric nervous system neuropathy</td>
<td>Prokinetic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(?) Gastric pacing</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>Sensory neuropathy</td>
<td>Tricyclics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(?) Neurostimulation</td>
</tr>
<tr>
<td>Persistent nausea</td>
<td>Tachygastria</td>
<td>Control of blood glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Domperidone</td>
</tr>
</tbody>
</table>

Owyang, C. “Phenotypic Switching in Diabetic Gastroparesis: Mechanism Directs Therapy.” *Gastroenterology*; 2011; 141 (4); 1134–1137
Autonomic Neuropathy (6)

Sudomotor

- Excessive coldness
- Blue/white skin discoloration
- Impaired sweating
- Dry and cracking skin
Autonomic Neuropathy
Sudomotor — QSART

Autonomic Neuropathy
Sudomotor — SudoScan
Neuropathic Cachexia (1)

- Onset with poor glycemic control
- More often older men, but can happen at any age
- Truncal involvement
- Depression
- Weight loss and pain go together
- Improves over weeks to months with tight glycemic control
- **Nutritional support is key**
- Pain control generally ineffective
Neuropathic Cachexia (2)

Ellenberg M. “Diabetic neuropathic cachexia.” *Diabetes* 1974; 23 (5): 418-423
Treatment-induced

- Onset with rapidly improving glycemic control
- Sudden onset of acute severe distal pain
- Pain control is generally ineffective
- Lasts months to a year
- Typically resolves with ongoing good glycemic control
- Can have long-lasting autonomic neuropathy
  - More common in Type 1
Radiculoplexopathy

- Onset more often with rapid weight loss
- Not related to glycemic control or duration of diabetes
- Acute onset of severe pain
- Often with sensory loss as well
- Proximal weakness near onset
- Muscle atrophy, distal deficits can persist
- Spreads over limb within days to weeks
- Can often spread to the other limb within weeks
  - Typically remains asymmetric
- More often involves lower limbs
- Treatment unclear
Radiculoplexopathy (2)
Radiculoplexopathy (4)

Radiculoplexopathy (5)

Other Mononeuropathies

- Thoracic radiculopathy
  - Painful thoracic dermatome
  - Typical pain control regimen
Other Mononeuropathies (2)

- Cranial neuropathies
  - Causes at least 10% of oculomotor palsies
  - Ptosis, impaired movement (“down & out”), diplopia, pain
Other Mononeuropathies (3)

- Cranial neuropathies
  - DM most common cause of trochlear palsy
  - Up and out; improves with positioning
Other Mononeuropathies (4)

- Compression neuropathies
  - 2% of the general population gets carpal tunnel syndrome
  - 14% of all diabetics do
  - 30% of diabetics with length-dependent polyneuropathy do
  - Obesity may play role as well
Other Mononeuropathies (5)

• Mononeuropathy
  • Vast differential, similar to polyneuropathy
  • Should evaluate for other causes as well
Poll: Neuropathy

Which type of neuropathy do your patients have?
A. Length-dependent neuropathy
B. Autonomic neuropathy
C. Acute episodic polyneuropathy
D. Radiculoplexopathy
E. Other mononeuropathy
F. Combination of the above
Questions

Thank You