Diabetic Neuropathy

Why Diabetic Neuropathy?

- Diabetes is the most common cause of peripheral neuropathy in the western countries
- There are 20.8 million Americans with diabetes mellitus
- Nearly one third are undiagnosed
- There are 54 million Americans who have pre-diabetes


Why Diabetic Neuropathy?

- Diabetic neuropathy is a major contributory factor in the pathogenesis of foot ulceration and Charcot joints
- 15% of diabetics develop foot ulcer during lifetime
What is Diabetic Neuropathy?

- A simple definition of DN for clinical practice is
  "The presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes"
  Boulton AJM et al. Diabet Med 1998

How common is diabetic neuropathy?

- A prospective study of 4400 patients found 8% had neuropathy at the time of diagnosis, and 50% after 25 years
  Pirart J. Diabetes Care 1978

- A landmark study of 380 diabetic subjects were evaluated for development and distribution of neuropathy
  Dyck PJ et al. Neurology 1993

The Rochester Diabetic Neuropathy Study

<table>
<thead>
<tr>
<th>Neuropathy type</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neuropathy</td>
<td>66%</td>
<td>59%</td>
</tr>
<tr>
<td>Distal neuropathy</td>
<td>54% (15%)</td>
<td>45% (13%)</td>
</tr>
<tr>
<td>CTS</td>
<td>33% (11%)</td>
<td>35% (6%)</td>
</tr>
<tr>
<td>Autonomic</td>
<td>7%</td>
<td>5%</td>
</tr>
<tr>
<td>Ulnar neuropathy</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>LSRPN</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

- About 10% of diabetic patients had neurologic deficits attributable to non-diabetic causes
  Dyck PJ et al. Neurology 1993

Staging Severity of Diabetic Neuropathy

- N0: No objective evidence of DN
- N1: Asymptomatic polyneuropathy
  N1a: No symptoms, no signs, abnormal test
  N1b: No symptoms, abnormal signs, abnormal test
- N2: Symptomatic neuropathy
  N2a: Symptoms, signs and test abnormality
  N2b: N2a plus significant ankle dorsiflexor weakness
- N3: Disabling neuropathy
The Rochester Diabetic Neuropathy Study

Risk factors for DPN
- Duration of diabetes
- The degree of hyperglycemia
- The presence of other microvascular complications is a marker for the presence of neuropathy rather than a risk factor *per se*


Diabetic Neuropathy Classification

Symmetric
- Diabetic distal polyneuropathy
- Diabetic autonomic neuropathy
- Polyneuropathy with glucose impairment
- Diabetic cachectic neuropathy
- CIDP in diabetes

Asymmetric
- Cranial neuropathies
- Mononeuropathies
- Radiculoplexus neuropathies
- Diabetic truncal radiculoneuropathy

Dyck PJ et al. Neurology 1993
### Symmetric Diabetic Neuropathies

- The most common form of diabetic neuropathy
- It is a length dependent, distal process
- It is very slowly progressive
- It is rarely disabling
- Sensory symptoms predominate
- Painful symptoms are present in about 10% of the patients
- Motor symptoms are usually minimal

### Diabetic Distal Symmetric Polyneuropathy

- Symptoms begin with sensory disturbance usually in the toes and feet
- With time, as symptoms progress to involve the calves, the hands may be affected
- Eventually may develop a “tear drop” pattern of loss over the anterior trunk
- In patients with hand symptoms early in the course, entrapment neuropathy is the likely cause

### Clinical examination tools:

- Pin prick test using a disposable pin
- Light touch using a cotton wisp
- Vibration test using 128Hz tuning fork
- Ankle reflex using a reflex hammer
- Pressure perception using 10 g monofilament may be used to assess the risk of ulceration
**Diabetic Autonomic Neuropathy**

- Usually accompanies mixed neuropathies
- Usually correlates with severity of somatic neuropathy
- Occasionally, occurs out of proportion to underlying neuropathy
- May involve cardiovascular, genitourinary, gastrointestinal, and/or thermoregulatory systems
- Common symptoms are orthostatic dizziness, erectile dysfunction, nausea, vomiting, bloating, abdominal pain, constipation or diarrhea, anhydrosis and hyperhidrosis.

Vinik AI et al. Diabetes Care 2003

**Polyneuropathy with Glucose Impairment**

- The neuropathy associated with IGT is milder than the neuropathy associated with newly diagnosed diabetes mellitus
- Small fiber involvement may be the earliest detectable sign of neuropathy

Sumner CJ et al. Neurology 2003

**Polyneuropathy with Glucose Impairment**

- Prospective study of 107 patients with idiopathic neuropathy found 13 of 107 had diabetes and 36 had IGT

Singleton JR et al. Diabetes Care 2001

**Diabetic Neuropathic Cachexia**

- Rare entity
- Acute painful neuropathy
- Associated with rapid, profound weight loss
- Occurs in the setting of poor glucose control
- Hypersensitivity and painful dyesthesias over the limbs and trunk
- Minimal sensory impairment
- Normal to near normal strength
- Prognosis is good

Ellenberg M Diabetes 1974; Jackson CE et al. J Neurol Neurosurg Psychiatry 1998
Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIPD) in Diabetes

- The possibility of increased incidence in diabetic patients is raised
- It is a gradually progressive disorder
- It is usually painless with proximal and distal arm and leg weakness
- Diagnosis is problematic

Comblath DR et al. Ann Neurol 1987
Gordon KC et al. Muscle Nerve 2002

Diabetic Mononeuropathies

- Diabetics are more susceptible to compression neuropathies
- Median neuropathy at the wrist (carpal tunnel syndrome)
- Ulnar neuropathy at the elbow
- Common peroneal neuropathy at the fibular head
- Lateral femoral cutaneous neuropathy (Meralgia paresthetica)

Stevens JC et al. Neurology 1988; Dyck PJ et al. neurology 1993

Asymmetric Diabetic Neuropathies

- Acute in onset
- Can be accompanied by severe pain
- Usually occurs after the age of 50
- CN III is the most common
  - Retroorbital pain
  - Diplopia, 2° to partial ophthalmoplegia
  - Pupil sparing


Cranial Neuropathies

- Acute in onset
- Can be accompanied by severe pain
- Usually occurs after the age of 50
- CN III is the most common
  - Retroorbital pain
  - Diplopia, 2° to partial ophthalmoplegia
  - Pupil sparing

Cranial Neuropathies

- CN IV and VI may also be affected
- Thought to be ischemic in nature
- Self limiting with symptoms resolving over months to a year

Lumbosacral Radiculoplexopathy

- Also known as diabetic amyotrophy, Bruns-Garland syndrome, or proximal diabetic neuropathy
- It affects older patients, usually after the age of 50, with Type 2 DM
- Glucose control is not a clear factor
- May be the presenting sign of diabetes (1/3)

Lumbosacral Radiculoplexopathy

- Presents with:
  - Severe pain in the back, hip, +/- thigh
  - Followed by proximal > distal leg weakness
  - Weight loss
  - Minimal sensory features
  - Onset usually unilateral; may progress to other leg

Lumbosacral Radiculoplexopathy

- Clinical examination:
  - Atrophy of the thigh
  - Patellar reflex abnormal (Achilles’ reflex +/-)
  - Strength difficult to assess 2° pain

### Diabetic Truncal Radiculoneuropathy

- Acute or subacute pain in one or more thoracic dermatomes “Shingles without the rash”
- Pain is stabbing or burning in nature
- Usually asymmetric
- Occurs after age 50
- Often diagnosed after fruitless and expensive abdominal evaluation and exploratory surgeries
- EMG useful

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### Red Flags

- Rapidly progressive symptoms
- Asymmetry
- Significant weakness
- Severe loss of position sense
- The presence of any of the above is an alert to look for other etiologies

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### What else should we know about diabetic neuropathy?

- Peripheral nerve involvement can present in a number of distinct syndromes
- Patient with diabetes mellitus can develop several types of peripheral nerve disorder at the same time
- Not all peripheral neuropathies occurring in patients with diabetes mellitus are due to the diabetes

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### Diabetic Peripheral Neuropathies: Part II

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March 2008
Diabetic Neuropathy

**Talk Outline**

- Why diabetic neuropathy?
- What is diabetic neuropathy?
- How common is diabetic neuropathy?
- Who gets diabetic neuropathy?
- How to recognize the different types?
- How to evaluate diabetic neuropathy?
- How does hyperglycemia causes peripheral neuropathy?
- How to treat it?
- What is the future prospective?

**Diagnostic Testing**

- Nerve conduction studies and electromyography are used to define the characteristics of the neuropathy (e.g. axonal, demyelinating) and the extent of neuropathy (e.g. distal length dependent; mononeuropathy; radiculopathy)
- Autonomic testing (tilt table, R-R variation) is usually reserved for patients with symptoms referable to the ANS (e.g. syncope or near syncope). Less useful for other autonomic symptoms (GI, GU)

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**Diagnostic Testing**

**Blood Work:**
- Fasting plasma glucose and hemoglobin A1c - screening tools and are useful for following glycemic control
- Two-hour glucose tolerance test - May be more sensitive in borderline cases
- Screening labs to rule out other etiologies – BUN, Cr, ANA, immunoelectropheresis and immunofixation, vitamin B-12, folate, T4 and TSH

**Quantitative sudomotor testing (QSART)**
- Small fiber neuropathy
- Helpful in documenting extent
- Following progression (research tool)
Diagnostic Testing

• Nerve Biopsies
  ✓ May confirm the presence of neuropathy.
  ✓ HOWEVER, there is little clinical use in the setting of DN
  ✓ Biopsies should be reserved for cases in which the etiology is in doubt
    • Could this be vasculitis?
    • Could this be amyloid?

Skin Biopsy

Diabetic Neuropathy

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**Hyperglycemia and Peripheral Neuropathy**

**Diabetes**

- Hyperglycemia
  - FA metabolism
  - DAG + PKC activation
  - Glycated products
  - Oxidative stress
  - Polyol pathway

  - Decrease blood flow
  - Hypoxia
  - Nerve conduction velocities
  - Degeneration of axon structure

**Vascular Pathogenesis of Diabetic Neuropathy**

- Temporal relationship of neuropathy, retinopathy, and nephropathy
- Retinopathy and nephropathy are associated with thickened basement membranes and narrowed endothelial lumens → microvascular pathology
- Perhaps, hypoxia or ischemia also play a role in neuropathy

**Diabetic Neuropathy Talk Outline**

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### Current Treatment of Diabetic Neuropathy

- Tight glucose control
- Foot care
- Symptomatic relief

### Diabetic Neuropathy: Therapy

#### Prevention

- Prediabetics or those with impaired glucose tolerance
  - FBG >100 and <126 or GTT >140 and <200
- Preliminary data from U of Michigan (2006) suggests that earliest signs of neuropathy may be reversible
  - Lifestyle changes (diet and exercise) resulted in improvement in QSART and nerve fiber density (skin biopsy)

#### Early diagnosis and Glucose Control

- DCCT study (1993) demonstrated 69% reduction in risk of diabetic neuropathy in patients with DM <5 years duration
- Glucose control has less impact on established neuropathy
## Foot Care
- Loss of sensation means that sores or injuries may go unnoticed, causing ulcers and/or infection to develop.
- 86,000 amputations a year related to diabetes. Some estimate that this number could be reduced by 50% with good care.

## Foot Care
- To decrease the risk of osteomyelitis (and amputation):
  - Inspect feet daily
  - Keep feet clean and dry
  - Wear light colored socks (to recognize blood or oozing more quickly)
  - Podiatric care

## Medications:
- FDA approved: Duloxetine (Cymbalta), Pregabalin (Lyrica)
- Anticonvulsants, antidepressants, antiarrhythmics, opioid-like drugs

## Physical therapy/Exercise:
- Beneficial for quality of life
- Range of motion
- Maintain mobility
- Sense of well-being
Treatment of Diabetic Neuropathy: Symptom Relief

• Other (????)
  • Anodyne therapy
  • Magnetic field therapy
  • Foot vibrating massager

Treatment of Diabetic Neuropathies

Caution!!
American Academy of Neurology issued a practice advisory June 2006:
  • Little or no data to support this treatment (surgical release)
  • Standard methods of nerve evaluations not included in the few published reports available
  • Need randomized controlled trials to evaluate this technique

Treatment of Diabetic Neuropathies

• Surgery:
  ✓ Decompression of nerves at known sites of narrowing or entrapment
  ✓ As of Jan 2006, 240 surgeons trained in this procedure. 1280 surgeries performed on 990 pts in International Neuropathy Decompression Registry

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### Treatment of Diabetic Neuropathy: Research Directions

- Goal is to develop treatments:
  - Reverse neuropathy
  - Change the rate of progression

### Diabetic Neuropathy: Future Therapies

- Despite these relative failures, ongoing trials with new agents are directed at:
  - Preventing or reversing oxidative stress
  - Preventing or accumulating glucose end products
  - Nerve growth factors

- Combinations of the above
- Verdict on these new approaches is not clear

### Treatment of Diabetic Neuropathy: Research Directions

- Most experimental approaches are aimed at one or more of the pathogenic models:
  - Alpha lipoic acid (oxidative stress)
  - Aldose reductase inhibitors (prevent accumulation of metabolic byproducts)
  - Nerve growth factors

### Image

- Relieves tired aching feet
- Stimulates circulation
- No electricity
- Stand on platform, insert coin

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15