Diabetic Neuropathy

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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**

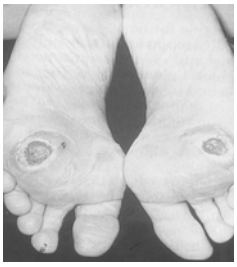
American Diabetes Association - http://www.diabetes.org

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?**

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 life time**



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

The Rochester Diabetic Neuropathy Study

Neuropathy type	Type 1	Type 2
Any neuropathy	66%	59%
Distal neuropathy	54% (15%)	45% (13%)
CTS	33% (11%)	35% (6%)
Autonomic	7%	5%
Ulnar neuropathy	2%	2%
LSRPN	1%	1%

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

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

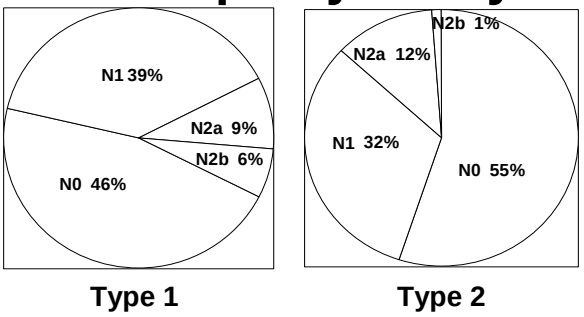
- **A landmark study of 380 diabetic subjects were evaluated for development and distribution of neuropathy**

Dyck PJ et al. Neurology 1993

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

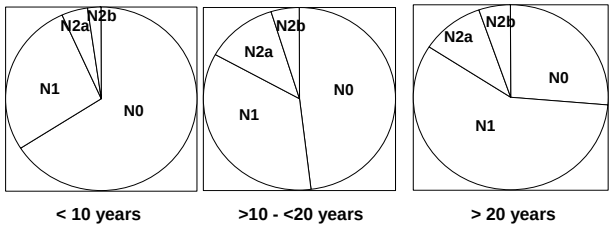


Risk factors for DPN

- **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***

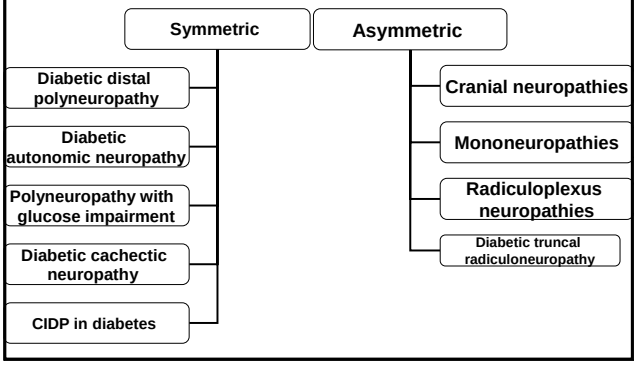
Dyck PJ et al. Diabetes Care 1992; Adler AI et al. Diabetes care 1997;
Van de Poll-Franse L et al. Diabet Med 2002

The Rochester Diabetic Neuropathy Study



Dyck PJ et al. Neurology 1993

Diabetic Neuropathy Classification



Symmetric Diabetic Neuropathies

Diabetic Distal Symmetric Polyneuropathy

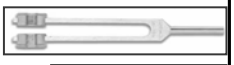
- Symptoms begin with sensory disturbance usually in the toes and feet
- With time, as symptoms progress to involve the calves, the hands may be affected
- eventually may develop a “tear drop” pattern of loss over the anterior trunk
- In patients with hand symptoms early in the course, entrapment neuropathy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

Diabetic Distal Symmetric Polyneuropathy

- 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

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**

Cornblath 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

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, 2^0 to partial ophthalmoplegia**
  - ✓ **Pupil sparing**

Asbury AK et al. Brain 1970; Smith BE et al. Ann Neurol 1992

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

Asbury AK et al. Brain 1970; Smith BE et al. Ann Neurol 1992

Lumbosacral Radiculoplexopathy

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

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)

Barhon RJ et al. Arch Neurol 1991

Lumbosacral Radiculoplexopathy

- Clinical examination:
  - ✓ Atrophy of the thigh
  - ✓ Patellar reflex abnormal (Achilles' reflex +/-)
  - ✓ Strength difficult to assess 2^{o} 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

Stewart JD. Ann Neurol 1989

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

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

Diabetic Peripheral Neuropathies: Part II

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March 2008

Diabetic Neuropathy Talk Outline

- Why diabetic neuropathy?
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- How does hyperglycemia causes peripheral neuropathy?
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- 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)

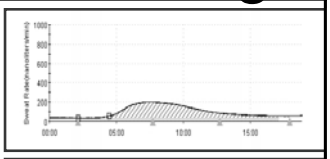
Diagnostic Testing

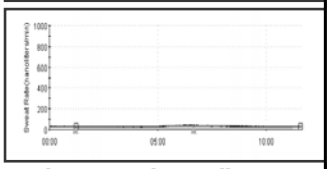
Blood Work:

- 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, T_4 and TSH

Diagnostic Testing

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

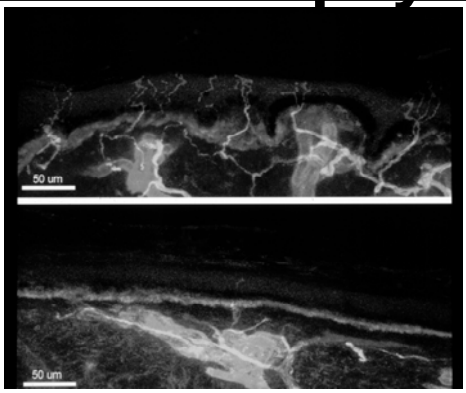




Diagnostic Testing

- **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



Diagnostic Testing

- **Skin biopsies**
  - ✓ **Useful in evaluating small fiber neuropathy**
  - ✓ **Research tool to evaluate potential therapies**

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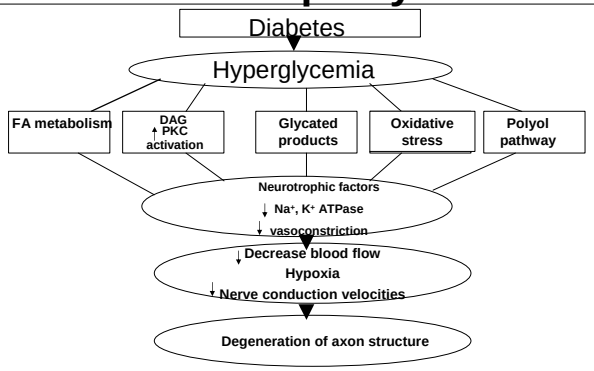
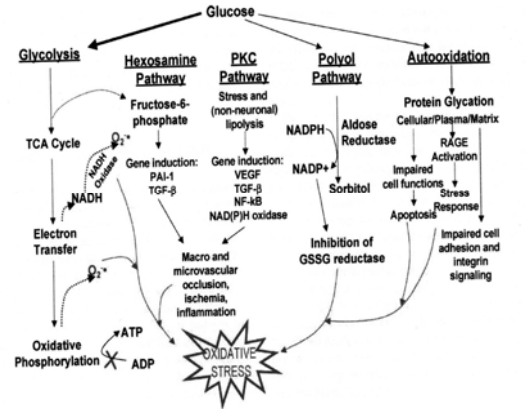
Hyperglycemia and Peripheral Neuropathy





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**

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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
- Prelim 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)

Diabetic Neuropathy: Therapy

Early diagnosis and Glucose Control

- DCCT study (1993) demonstrated 69% reduction in risk of diabetic neuropathy in patients with DM <u>≤5 years duration</u>
- Glucose control has less impact on established neuropathy

Treatment of Diabetic 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 # could be reduced by 50% with good care**

Treatment of Diabetic Neuropathy: Symptom Relief

- **Medications:**
  - ✓ **FDA approved: Duloxetine (Cymbalta), Pregabilin (Lyrica)**
  - ✓ **Anticonvulsants, antidepressants, antiarrhthymics, opioid-like drugs**

Treatment of Diabetic Neuropathy

- **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**

Treatment of Diabetic Neuropathy: Symptom Relief

- **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