Diabetic Neuropathy

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03/01/2016

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OBJECTIVES

- Burden of diabetic neuropathy
- Pathogenesis
- Risk factors
- Clinical presentation
- Diagnostic approach/Screening
- Prevention and Treatment
  - Peripheral Neuropathy
    - Screening
    - Management
  - Autonomic Neuropathy
    - Screening
    - Management

Burden of Diabetic Neuropathy

(86 million diabetics)

- Up to 50%
- >80% amp
  - 73,000 nc
  - adults ag
- 50% amp
- The total of $245 billion

Type 1 DM: 66% had neuropathy
Type 2 DM: 59% had neuropathy

PATHOGENESIS OF NEUROPATHY

Large afferent nerve fibers are proprioceptive and cold and vibration.
Small afferent fibers are responsible for conducting nociceptive stimuli, touch and warmth sensation.

Diabetic Peripheral Neuropathy

Healthy Nerves and Blood Vessels

Nerves and Blood Vessels Damaged by DPN


Diabetic Microneuritis, Microvascular Compromise, Nerve Blood Flow

Large fibers conduct proprioceptive and cold and vibration
Small fibers conduct nociceptive, temperature, touch

Fig. 2. Pathogenesis of diabetes neuropathy: the initiation and progression of diabetes.
GLYCEMIC INTERVENTION IN TYPE 1 VS TYPE 2 DM

<table>
<thead>
<tr>
<th>Trial</th>
<th>Length of study (yrs)</th>
<th>Baseline HbA1c (%)</th>
<th>Other outcomes</th>
<th>Reduced A1c mean (%)</th>
<th>Known CVD panel and complications</th>
<th>CVD panel and complications</th>
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</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>2.0</td>
<td>7.0</td>
<td>None</td>
<td>0.5</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Trial 2</td>
<td>1.5</td>
<td>8.0</td>
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<td>0.3</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Trial 3</td>
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<td>9.0</td>
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<td>0.7</td>
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<td>No</td>
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<tr>
<td>Trial 4</td>
<td>1.0</td>
<td>6.5</td>
<td>None</td>
<td>0.2</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Model for Change in HbA1c and complications

Tesfaye et al. NEJM 2005;341:533


Bennett K et al. Lancet Neurrol 2012;31:521-34
DIABETIC NEUROPATHY IS A DIAGNOSIS OF EXCLUSION

- Definition: “the presence of symptoms and/or sign of peripheral nerve dysfunction in people after the exclusion of other causes.”
- Causes of other neuropathy should be considered and excluded
  - Toxins (alcohol)
  - Neurotoxic medications (chemotherapy)
  - Vitamin B12 deficiency
  - Hypothyroidism
  - Renal disease
  - Malignancy (multiple myeloma,...)
  - Infection (HIV,...)
  - Chronic inflammatory demyelinating neuropathy
  - Inherited neuropathies
  - Vasculitis

SYMPTOMS OF DIABETIC PERIPHERAL NEUROPATHY
(MORE SENSORY THAN MOTOR)

- Numbness or loss of feeling (asleep or “bunched up sock under toes” sensation)
- Pricking/Tingling
- Aching Pain
- Burning Pain
- Stabbing Pain
- Unusual sensitivity or tenderness when feet are touched (allodynia)

CLASSIFICATION OF DIABETIC NEUROPATHY
### Screening

- All patients should be screened for diabetic neuropathy (DPN) starting
  - At diagnosis of type 2 diabetes
  - At 5 years after diagnosis of type 1 diabetes
  - At least annually thereafter

### How to Screen?

- **Screening**
  - Inspection
  - Assessment of foot pulses
  - Test for loss of protective sensation: 10-g monofilament plus testing any one of
    - Vibration using 128-Hz tuning fork
    - Pinprick sensation
    - Ankle reflexes
    - Vibration perception threshold
  - Combination of more than one test >87% sensitivity

### Assess for Risk Factors

- Previous amputation
- Past foot ulcer neuropathy
- Foot deformities
- Peripheral vascular disease
- Visual impairment
- Diabetic nephropathy
- Poor glycemic control
- Cigarette smoking
FOOT DEFORMITIES

Vibration perception tested with tuning fork.
MANAGEMENT OF DIABETIC NEUROPATHY

- Provide general foot care education (B)
- Use multidisciplinary approach
  - Individuals with foot ulcers, high-risk foot; especially prior ulcer or amputation (B)
- Refer patients to foot care specialists for ongoing preventive care, life-long surveillance (C)
  - Smokers
  - Loss of protective sensation or structural abnormalities
  - History of prior lower-extremity complications
  - Glycemic control
  - Prevention of trauma
  - Orthotics
  - Promptly treat skin ulcers or infections

MANAGEMENT OF NEUROPATHIC PAIN

- Education
- Dose titration
- Individualize treatment
- Combination therapy

Andrea et al. Nature Reviews Neurology 7, 573-583 (October 2011)
**Anticonvulsants**
- Gabapentin (level A evidence)
  - Dose: 300mg tid
  - Increase weekly by 300mg/d (max 3,600 mg/d)
- Pregabalin (level A evidence)
  - Dose: 75 mg bid
- Side effects: weight gain, peripheral edema, dizziness, somnolence
- Adjust dose for renal function
- Others: lamotrigine, oxcarbazepine, levetiracetam, tiagabine and zonisamide

**Tricyclic Antidepressants**
- Amitriptyline (level A evidence)
  - Dose: 25-100 mg/d
- Nortriptyline
  - Active metabolite of amitriptyline
- Side effects: dry mouth, weight gain, blurry vision, constipation, urinary retention, dizziness, drowsiness and cardiac arrhythmia
- Check levels in the elderly because of cardiotoxicity
- Other TCAs: desipramine, imipramine and clomipramine

**Serotonin-Norepinephrine Retake Inhibitors**
- Venlafaxine
  - Dose: 75-225 mg
- Duloxetine
  - Dose: 60-120 mg
- Side effects: dizziness, drowsiness, weight gain, hypertension, GI symptoms, and irritability
- Minimal anticholinergic adverse effects
- Tapentadol: inhibits norepinephrine uptake
  - FDA approved
_LOCAL AND REGIONAL TREATMENT_

- **Capsaicin**
  - One study found effective pain relief compared to amitriptyline
  - Other studies gave mixed results
  - Side effects: cutaneous burning, erythema, and sneezing

- **Lidocaine patch**
  - Indicated for post-herpetic neuralgia
  - Suggested efficacy in open studies of DPN
  - Common S/E: erythema and edema at treatment site

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<table>
<thead>
<tr>
<th>Local Analgesics</th>
<th>Local Anesthetic</th>
<th>Cautions</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capsaicin</td>
<td>Lidocaine patch</td>
<td></td>
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</tr>
<tr>
<td>Amitriptyline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naratriptan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziconotide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Xylocaine</td>
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</tbody>
</table>

**Table 3. Tailoring treatment to the patient**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-morbidities</td>
<td>TCAs</td>
</tr>
<tr>
<td>Glaucoma</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>TCAs</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>TCAs</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>Oxidemia</td>
<td>Pregabalin, gabapentin</td>
</tr>
<tr>
<td>Unsteadiness and falls</td>
<td>TCAs</td>
</tr>
<tr>
<td>Other factors</td>
<td>Duloxetine, pregabalin</td>
</tr>
<tr>
<td>Weight gain</td>
<td>TCAs, pregabalin, gabapentin</td>
</tr>
</tbody>
</table>

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**Evidence-based guideline: Treatment of painful diabetic neuropathy**

Neurology® 2011; 76: 1–11
DIABETIC AUTONOMIC NEUROPATHY

- Major clinical manifestation include:
  - Hypoglycemia unawareness
  - Cardiovascular, gastrointestinal, urogenital, sudomotor dysfunction (sweating)

CARDIAC AUTONOMIC NEUROPATHY

- Screening for signs and symptoms of cardiovascular autonomic neuropathy
  - Should be instituted at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes
  - Special testing rarely needed; may not affect management or outcomes (E)

RECOMMENDATIONS:
AUTONOMIC NEUROPATHY SCREENING
CARDIAC AUTONOMIC NEUROPATHY: SCREENING
- Heart rate changes
  - Resting heart rate > 100 BPM
  - Decreased heart rate variability (<10 bpm is abnormal)
- Orthostatic hypotension
  - A fall in systolic and diastolic blood pressure >20 mmHg and >10 mmHg respectively
- Exercise intolerance
- Silent ischemia
- Loss of circadian patterns

CARDIAC AUTONOMIC NEUROPATHY: RISKS
- CAN is associated with mortality independently of other cardiovascular risk factor
- May be completely asymptomatic

CV AUTONOMIC NEUROPATHY: MANAGEMENT
- Non-pharmacologic approach
  - Increasing consumption of water
  - Lower extremity stockings
  - Graded supervised exercise
  - Can be aggravated by TCA
- Pharmacologic approach
  - Pyridostigmine
  - Beta blockers
  - Midodrine
  - Others: fluoxetine, erythropoietin, octreotide
- Glycemic control


Gynecologic Care, Volume 29, Number 4, April 2009
American College of Obstetricians and Gynecologists
Diabetic Neuropathies: A statement by the American Diabetes Association. DIABETES CARE, VOLUME 28, NUMBER 4, APRIL 2005
ADA Diabetic Neuropathies. Diabetes Care 2005. 28:956-962
GASTROINTESTINAL DISTURBANCE

- Clinical manifestation
  - Gastroparesis
  - Esophageal dysmotility
  - Constipation
  - Diarrhea
  - Fecal incontinence
- Gastroparesis should be suspected in individuals with erratic glucose control

Evaluation:
- Barium studies
- Endoscopy
- May lead to poor glycemic control, quality of life, nutritional compromise
- Exacerbated by hyperglycemia

GASTROPARESIS

- Bloating
- Anorexia
- Early or prolonged satiety
- Upper abdominal distension
- Epigastric discomfort
- Postprandial nausea and vomiting of undigested food

GASTROPARESIS: MANAGEMENT

BLADDER DYSFUNCTION

- Clinical manifestations
  - Suprapubic fullness
  - Frequency, hesitancy
  - Nocturia
  - Poor stream
  - Urinary retention and overflow incontinence
- Evaluation should be performed in those with
  - Urinary tract infections
  - Pyelonephritis
  - Incontinence
  - Palpable bladder
  - Erectile dysfunction/retrograde ejaculation

ADA Diabetic Neuropathies. Diabetes Care 2005. 28:956-962

THERAPY OF BLADDER HYPOMOTILITY

- Behavioral therapy
- Compressive and reflex maneuvers
- Catheterization and collecting devices
- Pharmacotherapy
- Electrical stimulation
- Surgery

ERECTILE DYSFUNCTION IN MEN WITH DIABETES

SUDOMOTOR NEUROPATHY

- Hyperhidrosis / Heat intolerance in the upper torso
  - may be linked with certain foods particularly spicy foods and cheeses.
  - Antimuscarinics (atropine/scopolamine)
- Anhidrosis in the lower extremities
- True temperature elevation is rare
- Pruritis
- Extremities may appear:
  - Thin
  - Hair loss
  - Dryness and flaking
  - Callus and nail dystrophies
- These skin changes increase the risk for ulceration
- Therapies—emollients, scopolamine, vaso-dilators, botulinum toxin, glycopyrrrolate

CONCLUSION

- There is more to neuropathy than diabetic peripheral neuropathy
- The key is to be alert various neuropathy and their variable manifestation
- Ask patients and do appropriate screening
- Initiate appropriate diagnostic workup
- Targeted therapies
GASTROPARESIS: DIAGNOSTIC TOOLS

- Measure gastric emptying
  - Scintigraphic determination of emptying solid meal
    a normal value is 27%–80% at 1 h, 80–90% at 2 h and 0–10% at 4 h
  - Gastric emptying breath test (13C)
- Capsule study
- Imaging
  - MRI, SPECT, ultrasonography
- Antroduodenal manometry and barostat
- Electrogastrography

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GI DAN: CONSTIPATION

- Affecting nearly 60% of diabetic patients
- Associated with atony of the large bowel and rectum and sometimes with megacolon
- Bouts of constipation may alternate with episodes of diarrhea.
- Rule out other causes such as hypothyroidism, side effects of drugs such as amitriptyline or calcium channel blockers, and colonic carcinoma
- Anorectal manometry may be used to assess the rectal anal inhibitory reflex
- Tx: Sorbitol and lactulose, intermittent use of saline or osmotic laxatives, octreotide

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**GI DAN: Diabetic Diarrhea**

- Affects 20% of diabetic patients
- Increased intestinal motility and secretion caused by diminished sympathetic inhibition
- Associated with bacterial overgrowth
- Exocrine pancreatic insufficiency
- Steatorrhea (fat malabsorption)
- Bile-salt malabsorption
- Anorectal dysfunction - lowered rectal sensory threshold, weak internal anal sphincter
- Concurrent celiac sprue - similar genetic predisposition

*Pancreatology 2003;1:395-402*

**Diabetic Diarrhea: Workup**

- Rule out medication confounders (metformin, acarbose)
- Stool analysis
- Barium study
- Endoscopy/colonoscopy
- Breath test
- Manometry
- Test for bile acid malabsorption, pancreatic insufficiency
- Metronidazole
- Clonidine
- Cholestyramine
- Loperamide
- Octreotide


**Genitourinary DAN**

- Neurogenic bladder
  - Impaired parasympathetic innervation
  - Bladder hypotonia, incomplete bladder emptying, dribbling and overflow incontinence.
  - Diagnosed by post void residuals of >150 cc
  - Therapies
    - Bethanechol
    - Alpha blockers
    - Catheterization or indwelling catheter.
- Retrograde Ejaculation
  - Damage to the efferent sympathetic nerves coordinating simultaneous closure of internal vesicle sphincter and relaxation of the external vesicle sphincter during ejaculation
  - Absence of sperm in semen and presence of sperm in urine
  - A concern if fertility desired
GENITOURINARY DAN: ERIK DYSFUNCTION

> In 50-75% of DM men
> Female dysfunction
> Incidence increases from 5%
> Can occur within 10 years of
> Often multifactorial
> Autonomic ED is accompanied
> reflexes and loss of vibration
> Most often occurs without a
> marker for vascular disease

TAKE HOME POINTS

> More to neuropathy than DPN
> Be aware of neuropathy at its variable manifestations
> Screen
> Initiate appropriate diagnostic workup
> Targeted therapies

NEUROPATHY IS A COMMON COMPLICATION OF DM

### Classification of Neuropathy

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
<th>Signs on exam</th>
<th>Testing</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Lumbosacral Radiculoplexopathy aka diabetic amyotrophy</td>
<td><strong>Severe unilateral pain in back, hip, or thigh</strong> • Spreads to other side within weeks to months • Weight loss • Weakness usually in proximal leg muscles, also distal • May spread to UE</td>
<td><strong>Weakness of hip, knee, ankle muscle groups</strong> • Profound atrophy of thigh, also distal LE • Distal sensory loss • Loss of knee/ankle reflexes</td>
<td><strong>NCS</strong>-similar to DPN, assymetrical effect on femoral group <strong>EMG</strong>-many fibrillation potentials in leg and lumbosacral paraspinous muscles <strong>Hi CSF protein</strong> <strong>Hi ESR</strong> <strong>MRI</strong>-nerve root enhancement</td>
<td><strong>Pain control</strong> • <strong>Glucose control</strong> • <strong>PT</strong> • Months to recover • May have residual weakness</td>
</tr>
<tr>
<td>Truncal radiculopathy</td>
<td><strong>Abrupt pain over days to weeks</strong> • Trunk, thorax, abdomen • Severe dysesthesias • Dermatome pattern—can be multiple; unilateral or bilateral</td>
<td></td>
<td></td>
<td><strong>Pain management</strong> • Lasts weeks–months, gradual resolution</td>
</tr>
<tr>
<td>Cranial neuropathies</td>
<td><strong>Sudden</strong> • CN III, IV, VI, VII • Unilateral • Retroorbital pain</td>
<td><strong>Sparing of pupil</strong> Imaging to r/o stroke</td>
<td></td>
<td><strong>Glucose control</strong> • Recovery in 2–3 mo</td>
</tr>
<tr>
<td>Isolated mononeuropathies</td>
<td><strong>Carpal, ulnar, peroneal at fibular head</strong> • Lateral cutaneous</td>
<td><strong>NCS</strong></td>
<td><strong>Rest</strong> • <strong>Splints</strong> • <strong>Diuretics, Pasnoor M, et al. Neurol Clin 31 (2013) 447–462</strong></td>
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</table>
MANAGEMENT OF NEUROPATHIC PAIN

CLASSIFICATION OF NEUROPATHY

Generalized symmetric polyneuropathy
Focal and multifocal neuropathies
Autonomic neuropathy
GI AUTONOMIC NEUROPATHY AFFECTS UP TO 75% DM PATIENTS

Gastroparesis and Glycemic Control

Fig. 1. Typical kinetics of plasma emerging after intragastric dose in patients with and without autonomic neuropathy. Area under the curve (AUC) reflects the degree of autonomic dysfunction.