Diabetic Neuropathies
Clinical Presentations and Approaches to Therapy

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Objectives
At the conclusion of this presentation, participants will be able to:
1. Recognize common manifestations of diabetic neuropathies including symmetric polyneuropathy, lumbosacral plexopathy, and mononeuropathies
2. Identify motor, sensory, and autonomic manifestations of diabetic neuropathies
3. Determine appropriate diagnostic modalities on the basis of clinical presentation
4. Develop an appropriate focused management strategy incorporating clinical and diagnostic findings

Prevalence
• Diabetes mellitus – 6% of US population
• Neuropathy in diabetes mellitus – 30%
  – 7.5% at disease onset
  – 50% after 25 years
  = ~ 2% of US population suffers from diabetic neuropathy

Risk factors
• Poor glycemic control
  – Higher HbA1c
• Cardiovascular risk factors
  – Hypertension
  – Smoking
  – Obesity
  – Hypertriglyceridemia
• Presence of cardiovascular disease

Pre-diabetic conditions
• Impaired glucose tolerance (IGT)
  – 2-hour glucose tolerance test – 140 to 199 mg/dL at 2 hours
• Impaired fasting glucose (IFG)
  – Fasting plasma glucose – 100 to 125 mg/dL
• HbA1c 5.7 to 6.4%
Neuropathy
• Pourhamidi et al
  – no difference in large and small nerve function in patients with IGT and those with NGT
• Singleton et al
  – increased prevalence of IGT in patients with painful sensory neuropathy
• Ziegler et al
  – slight increase in prevalence of polyneuropathy in patients with IGT and IFG
• Summary – pre-diabetic conditions are likely associated with an increased incidence of polyneuropathy, primarily painful sensory neuropathy

Symmetric neuropathies
• Chronic
  – Distal sensorimotor / autonomic
  – Autonomic
• Acute
  – Painful
  – Reversible
Chronic Distal Sensorimotor / Autonomic

- Most common type of diabetic neuropathy
- “Diabetic Neuropathy”
  - Symptomatic evidence
    - 4-10% at 5 years
    - 13-15% at 25 years
    - Mean – 8 years after onset of diabetes
  - Objective evidence
    - 65-80% of all diabetics

Risk factors

- Increased
  - Age
  - Body weight
  - Height
  - Disease duration
  - HbA1c
  - Triglycerides
  - Smoking
- Type I diabetes
  - Poor glycemic control
- Type II diabetes
  - Metformin treatment – associated with low B12 and more severe neuropathy

Clinical features

- Sensory loss
  - Painless, occasionally small- or large-fiber selective
  - Associated with foot ulcers in chronic diabetes
    - 7-fold increase
- Discomfort
  - Pain, burning, fatigue
  - Usually distal
- Weakness
  - Mild or absent
  - Distal legs
- Autonomic involvement
  - Sympathetic denervation – increased peripheral blood flow
  - Cardiac denervation

Criteria for diagnosis

- Michigan Neuropathy Screening Instrument
  - Appearance of feet (each foot)
    - Deformed, dry skin, callus, infection, fissure
    - Score one if any of these features are present
  - Ulceration (each foot)
    - Score one if present
  - Ankle reflexes (each foot)
    - 1/4 (reinforcement) = 0.5 points
    - Absent = 1 point
  - Vibration perception at great toe (each foot)
    - Reduced (< 10 seconds) = 0.5 points
    - Absent = 1 point
- A score of 2 or greater has a specificity of 95%, sensitivity of 80%

Associated Conditions

- Restless Legs Syndrome (RLS)
- Painful Legs Moving Toes syndrome (PLMT)
- Nocturnal leg cramps

Complications

- Foot ulceration
  - Acute ulcers secondary to poorly fitting shoes
  - Chronic plantar ulcers over weight-bearing areas
  - Likely multifactorial (neuropathy, autonomic dysfunction, vascular insufficiency)
- Foot amputation
  - Diabetic neuropathy contributes to over 60% of lower extremity amputations in patients with diabetes
  - Structural changes in the feet secondary to atrophy of the intrinsic foot musculature
    - hammertoe deformities
- Charcot’s joints (Neuropathic osteoarthropathy)
  - Onset 50-65 years, occasionally acute
  - Foot 80%, ankle 10%
  - Associated with
    - Poorly controlled insulin-dependent diabetes
    - Osteopenia
    - X-rays
      - Bone & joint destruction
      - Calcific deposits around joint
Laboratory features

- Electrodiagnostic testing
  - Reduced sensory amplitudes
  - Normal or mildly reduced conduction velocities

- Pathology
  - Axon loss / regeneration

Chronic Autonomic

- Most common cause of autonomic neuropathy in developed countries
- Multiple autonomic systems involved (parasympathetic and sympathetic)
- Typically associated with distal sensorimotor neuropathy
  - Subclinical may occur within years, earlier in type II diabetes
- Increased risk:
  - Duration of diabetes
  - High HbA1c
  - Increased age
  - Obesity
- Long-term
  - Overall mortality increased
  - Mortality with cardiovascular autonomic neuropathy
    - 27-56% over 5-10 years
  - Increased incidence of painless myocardial infarction

Autonomic Manifestations

- Genito-urinary
  - Erectile dysfunction – 30-75%
  - Voiding dysfunction – up to 50%
- Cardiovascular
  - 20% of asymptomatic diabetics
  - Postural hypotension – 17 – 43%
  - Reduced R-R interval variation / increased heart rate = parasympathetic dysfunction
- Gastrointestinal
  - Gastroparesis
  - Constipation – up to 80%
  - Hypoglycemia (sympathetic innervation inhibits insulin release)
- Sudomotor
  - Hypohidrosis – loss of thermoregulation
  - Gustatory sweating – excessive facial sweating in response to food
  - Foot hypohidrosis – ulcers, fissures, cracks

Acute Painful

- Associated with:
  - Poorly controlled diabetes
  - Rapid weight loss
    - Unintended = diabetic neuropathic cachexia
    - Intentional = diabetic anorexia
  - Burning & hypersensitivity in the feet, may be severe
  - Mild changes in sensation / reflexes
  - Improves with better control of diabetes and weight gain.

Acute Reversible (Treatment Induced)

- Insulin Neuritis
- Initiation of insulin / oral hypoglycemics
- Neuropathy associated with reduction in HbA1c
  - 3% reduction = 60% frequency of neuropathy
  - 6% reduction = 100% frequency of neuropathy
- Onset within one month of initiation of treatment
- Monophasic – symptoms improve with continued glycemic control
  - 50% improvement in pain in 12 to 28 months

Acute Reversible (Treatment Induced)

- Clinical
  - Pain – hyperalgesia, allodynia
  - Distal extremity, occasionally diffuse, often severe
  - Sensory loss
    - Pan-modal, especially small-fiber
  - Autonomic
- Laboratory
  - NCS – abnormalities may persist after symptomatic resolution
Asymmetric neuropathies

- Lumbosacral plexopathy
- Truncal Neuropathy
- Mononeuropathies
  - Cranial
  - Peripheral

Lumbosacral plexopathy

- Diabetic amyotrophy
  - i.e. Diabetic Lumbosacral Radiculoplexus Neuropathy (DLRPN)
  - i.e. Bruns-Garland Syndrome
- Non-DLRPN

DLRPN

- Older patients with type II diabetes mellitus
- NOT related to glycemic control
- Typically seen in patients with shorter disease duration than diabetic neuropathy
- Clinical presentation
  - Abrupt onset of severe unilateral thigh pain
  - Followed by progressive atrophy and weakness
  - Contralateral limb involved in most patients within several months
  - Most patients have significant weight loss and become wheelchair-dependent
  - Preferentially affects the femoral nerve – frequently mislabeled as a femoral neuropathy
  - Associated with mild upper extremity involvement; some patients have more severe upper extremity symptoms

Diagnosis
- Clinical presentation
- Electrodagnostic testing (demonstrates a polyradiculoneuropathy)
- Nerve biopsy (not required for diagnosis) - microvasculitis

Treatment
- Not definitively shown to respond to immunotherapy
- IV Ig / IV corticosteroids may hasten recovery
- Progression
  - Progression over several months with subsequent improvement
  - Most patients are left with permanent deficits

Non-DLRPN

- Nearly identical to DLRPN
- Clinical features
  - Diagnostic testing (including nerve biopsy)
- Prognosis

Many patients with non-DLRPN have evidence of impaired glucose tolerance:\n
- 2-hour GTT
- Only a small minority of patients develop diabetes mellitus:\n
\[1\] Kelkar et al 2005
\[2\] Dyck et al 2001

Truncal Neuropathy

- Occasionally is the first manifestation of diabetes (type I or II)
  - More common in type II diabetes
  - Clinically similar to herpes zoster (sine herpete)
- Acute or subacute pain, paresthesias, and allodynia in the abdominal or chest wall
- Bilateral in up to 50%
- Examination
  - Sensory loss or hyperesthesia
    - May have unilateral abdominal swelling due to localized weakness (possible herniation)
- EMG typically reveals denervation in abdominal musculature / thoracic paraspinal musculature
- Natural history is gradual improvement and return to baseline
- Pain may be difficult to manage
Mononeuropathies

- **Cranial Nerves**
  - Most common in older type II diabetics
  - 3rd nerve most common
    - Sudden onset
    - Retro-orbital pain
    - Pupil sparing
    - Recovery within weeks to months
  - 7th nerve occasionally involved (Bell's Palsy)

- **Limb**
  - Damage at common compression sites
    - Carpal tunnel syndrome
    - Ulnar neuropathy
    - Tarsal tunnel syndrome
    - Vascular lesion
    - Abrupt & painful

CIDP

- **Chronic Inflammatory Demyelinating Polyradiculoneuropathy**

  - Controversial relationship between CIDP and diabetes
  - Reported increased incidence of CIDP in patients with diabetes
    - 11-fold increased risk
  - Subsequently found to likely owe to electrodiagnostic features of diabetic neuropathy meeting diagnostic criteria for CIDP
    - Noted that a small effect could not be excluded
  - Significant improvement may be seen with immunotherapy (e.g. IVIg)

Summary

- Obtain electrodiagnostic testing
- If diagnostic criteria for CIDP are met, initiate a trial of immunotherapy

1Sharma et al 2002
2Laughlin et al 2009
3Jann et al 2009

Diagnostic Evaluation

- Early recognition allows for strategies to prevent complications such as falls and ulceration
- Early diagnosis facilitates effective therapy
- Exclude contributing comorbid conditions
  - Lumbosacral radiculopathies
  - Vascular insufficiency

Diagnostic Testing

- Laboratory Testing
- Electrodiagnostic Testing
- Autonomic Function Testing

Laboratory Testing

- 50% of patients with diabetic polyneuropathy have at least one additional potential cause / contributing condition
  - 50% apparent through careful history
    - Alcoholic neuropathy
    - Toxic neuropathy
  - Laboratory evaluation
    - B12 / methylmalonic acid
    - SPEP/IFE
    - Thyroid dysfunction
    - Evaluation for connective tissue disease / infection in at-risk patients

1Gorson KC, Ropper AH 2006.

Electrodiagnostic Testing

- Toronto Consensus Conference, 2009
  - Confirmed diabetic neuropathy requires abnormal electrodiagnostic testing with symptoms or signs
  - Validated measures of small-fiber function (epidermal nerve fiber density, autonomic function testing) may be used in patients with normal electrodiagnostic testing.
  - Probable clinical requires both symptoms and signs
- AAN / AANEM / AAPMR Practice Parameter (2009)
  - Autonomic testing should be considered in the evaluation of patients with polyneuropathy

1Tesfaye S et al, 2010
2England JD et al 2009
Autonomic Function Testing

• Cardiovascular
  – Heart rate variability (deep breathing, postural change)
  – Tilt table testing
• Gastrointestinal
  – Gastric emptying study
• Genitourinary
  – Postvoid residual
• Sudomotor
  – Quantitative sudomotor axon reflex testing (QoSART)
  – Epidermal nerve fiber density (ENFD)

Heart Rate Variability

Management

• Optimize glycemic control
• Assess for contributing medical conditions
• Provide symptomatic management
  – Fall prevention
  – Neuropathic pain
  – Dysautonomia

Glycemic Control

• Enhanced glycemic control1
  – Prevents the development of clinical neuropathy in type I diabetes
  – Reduces nerve conduction abnormalities
  – Improves clinical sensory findings (vibration threshold)
• Symptomatic diabetic neuropathy is generally not reversible.
• May have progression despite attempts at glycemic control.

1Callaghan et al 2012

ADA recommendations

• Screen for neuropathy in diabetic patients
  – At diagnosis of type II
  – Five years after diagnosis of type I
• After initial screening, screen at least annually
  – Examine sensory function in the feet
• Careful clinical examination annually
• Regular diabetic foot examination
• Encourage the patient to inspect his or her feet daily

Glycemic Control

• Increased risk of falls with
  – Increased age
  – History of falls
  – Evidence of impaired balance on examination
    • Impaired proprioception at the great toe
    • Impaired Romberg’s
• Consider referral to physical therapy for
  – Gait retraining
  – Recommendations regarding use of a gait assistive device
    • Quad-cane
    • Rolling walker

Fall Prevention
Neuropathic Pain

- Sensory symptoms
  - Positive – “Feels numb”
  - Paresthesias
  - Pain
  - “Abnormal” sensation (dysesthetic)
- Negative – “Is numb”
  - Overt sensory loss
- Positive sensory symptoms respond to symptomatic management

Neuropathic Pain
AAN Treatment Guidelines, 2011

- Effective
  - Pregabalin 300 to 600mg daily
- Probably effective
  - Gabapentin 900 to 3600mg daily
  - Valproate 500 to 1200mg daily
  - Amitriptyline 25 to 150mg daily
  - Duloxetine 60 to 120mg daily
  - Venlafaxine 75 to 225mg daily
  - Dextromethorphan 400mg daily
  - Morphine up to 120mg daily
  - Oxycodone, mean 37mg daily, maximum 120mg daily
  - Tramadol 210mg daily
  - Capsaicin 0.075% 4x/day

\[1\] Brill V et al 2011

Dysautonomia

- Cardiovascular
  - Make changes in posture slowly
  - Oral pharmacotherapy
    - Fluorocortisone
    - Midodrine
  - Side effects may be prohibitive
- Gastrointestinal
  - Treatment of gastroparesis

Sources

1. Boulton AJ et al 2005
Sources

- Pourhamidi K, Dahlin LB, Englund E, Rolandsson O. No difference in small or large nerve fiber function between individuals with normal glucose tolerance and impaired glucose tolerance. Diabetes Care 2013 Apr;36(4):982-4.