

Pain Management in Diabetic Neuropathy

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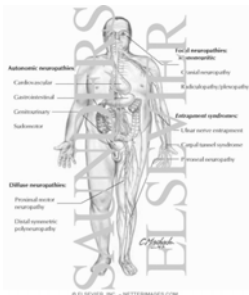


Objectives

- Define diabetic peripheral neuropathy.
- Describe three common perceptions/complaints related to diabetic peripheral neuropathy.
- Identify three interventions for diabetic peripheral neuropathy.

Peripheral nervous system

- Autonomic NS- involuntary
- Sensorimotor- send info from skin/organs
- Motor nerves- commands from brain to body



Diabetic Peripheral Neuropathy

Definition:

“ a demonstrable disorder, either clinically evident or subclinical, that occurs in the setting of diabetes without other causes . The neuropathic disorder includes manifestations in the somatic (voluntary) and /or autonomic (involuntary)parts of the peripheral nervous system. “

Consensus Statement. Report and recommendations of the San Antonio conference on diabetic neuropathy. Diabetes Care. 1988;11:592-7

Diabetic Neuropathy

Prevalence: 10-90%
Most common complication of diabetes
accounting for more hospitalizations than
All other complications combined
Accounts for 50-75% of
nontraumatic amputations

<http://diabetesmanager.pbwiki.com/Diabetic-Neuropathies#Definition>

Incidence of Diabetic Neuropathy

- Occurs with similar frequency in those with type 1 and type 2.
- Prevalence*
 - 8% at diagnosis.
 - 50% after 25 years.
 - Type 1 related to duration and severity of hyperglycemia.
 - Type 2 may present at diagnosis with symptoms of neuropathy d/t presence of undiagnosed DM for years.

* Pirat's study, 1978

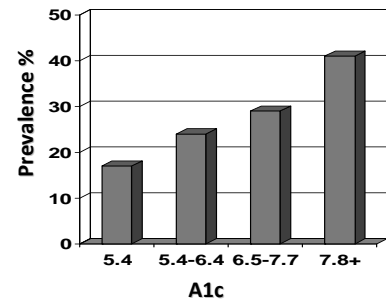
Diabetic Neuropathy: "The Forgotten Complication"

- Results of the 2005 ADA National Survey¹
 - Only 1 in 4 respondents who experience symptoms of DN have been diagnosed with the condition
 - 56% of respondents who experience symptoms remain unaware of the term "diabetic neuropathy"
 - 62% believe that their symptoms are associated with their diabetes, but only 42% have been told by their PCP that diabetes is the cause
 - Approximately 1 in 7 people who said they talked to their PCP about their symptoms and pain reported that no cause was mentioned.

1. May 10, 2005 / PR Newswire via COMTEX

Risk Factors for DPN: Glycemic Control EURODIAB Type 1 DM Neuropathy Study

- Data adjusted for duration of diabetes
- Prevalence of DN: 30% and is related to A1c (P<0.001)



Tesfaye S., et al. *Diabetologia*. 1996; 39:1377-1384

Metabolic Control /Lifestyle Risk Factors

- Hyperglycemia (chronic)
- Duration of diabetes
- Age
- Cigarette smoking
- HTN
- Hyperlipidemia
- BMI
- Alcohol

Etiology of Nerve Damage

- Role of Hyperglycemia
 - Poly Pathway
 - Glycation of various nerve proteins
 - Oxidative Stress
- Amino-acid uptake and protein synthesis
- Vascular abnormalities
- Blood abnormalities
- Nerve regeneration
- Other factors

Mechanisms of Neuropathic Pain






- Ectopic generation of nerve impulses
- Dorsal root ganglion hyperactivity
- Abnormal pain transmission within CNS
- Haemodynamic changes
- Alterations in blood flow
- Disruption in neural pathways and neurotransmitters

- More than one mechanism of action likely involved in neuropathic pain
- Ability to infer mechanisms from signs/symptoms may help target therapy better.

Peripheral Neuropathies

Classifications of Diabetic Neuropathies

1. Progressive
 - a. Distal Symmetrical polyneuropathy
 - b. "Small fibre" neuropathy
2. Reversible
 - a. Mononeuropathies
 - b. Acute diffuse painful neuropathy
3. Pressure Palsies
 - a. Median nerve (carpal tunnel)
 - b. Ulnar nerve
 - c. Lateral popliteal nerve (rare)

Symmetrical diffuse sensorimotor neuropathy	Acute diffuse painful neuropathy	Femoral neuropathy (amyotrophy)	Other acute mononeuropathies	Pressure palsies
				
Sensory loss O →+++ Pain →+++ Tendon reflexes N→↓ Motor deficit O→+	Sensory loss O →+ Pain →+++ Tendon reflexes N→↓ Motor deficit O	Sensory loss O →++ Pain →+++ Tendon reflexes ↓→O Motor deficit →+++	Sensory loss O →+ Pain →+++ Tendon reflexes N Motor deficit →+++	Sensory loss →+++ Pain →++ Tendon reflexes N Motor deficit →+++

Watkins J, Edmonds M: Clinical Features of diabetic neuropathy. Textbook of Diabetes. 1997/Volume 2; Section 12; p 50.3

Distal symmetrical polyneuropathy (chronic sensorimotor neuropathy)

- Most common
- Seen in both type 1 and type 2
- Affects 30% of hospital based
- 23% of community
- Incidence is about 2% per year
- Predominantly sensory
- Autonomic involvement common (asymptomatic)
- Clinical motor involvement very rare
- No recovery

Symptoms

- Asymptomatic
- Numbness , loss of pain sensation
- Altered sensation
 - Paraesthesiae
 - Dysthesione
 - allodynia
- pain



Signs

- May be no abnormal signs
- Wasting and weakness are rare
- Sensory Loss
 - Pain and thermal initially

Diffuse Small-Fiber Neuropathy

- Pain is burning and superficial and often allodynia
- Late in condition- lack of sensation (hypoalgesia)
- Defective warm thermal sensation
- Defective autonomic function with decreased sweating, dry skin, impaired vasomotion and blood flow and a cold foot

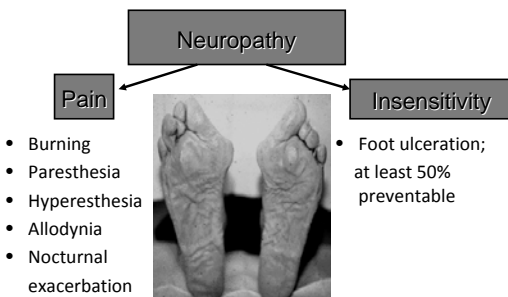
Consequences of Progressive neuropathies

Can also cause muscle weakness and loss of reflexes (ankle)

- Causes changes in gait
- Foot deformities (hammertoes, bunions, Charcot's foot)

Minor injuries (blisters and sores) can get infected, ulcerate and require amputation.

Clinical Consequences of DPN



Foot Deformities



Mononeuropathies

- Single nerves or their roots
- Occasionally groups of nerve roots
- Rapid, severe onset
- Eventual recovery
- Occur predominantly in older, males
- Unrelated to other diabetic complications
- Important to rule out other causes of nerve damage or nerve root compression

Truncal Radiculopathies

- Pain affects area of trunk
- Unilaterally or bilaterally
- Weakness of abdominal wall muscles (rare)
- Recovery less than 6 months
- Muscle bulging resolves

Bulging of left lower abdomen



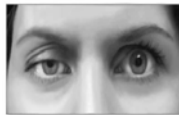
Cranial Nerve Palsies

Ocular palsies due to lesions
3rd and 6th cranial nerves

Onset of diplopia is abrupt
Preceded by pain behind or just
above the eye

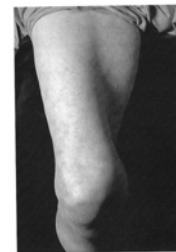
Recover usually within 3 months, relapse rare

Ptosis (drooping of the eyelid)



Proximal Motor Neuropathy (femoral neuropathy or amyotrophy)

- Pain in thigh to below knee
- With or without wasting of thigh
- Insomnia
- Depression
- Unilateral or bilateral
- Recovery is slow 12 months
- Pain ↓ after 3 months
- Rule out CIPD



Acute diffuse painful neuropathy

- Severe pain
- Cachexia
- Weight loss
- Depression
- Erectile dysfunction
- Both type 1 and 2
- Recovery within one year

Signs and Symptoms

- Pain described as
 - Electric shocks
 - Shooting
 - Searing
 - Burning, like walking on hot sand
 - Pins and needles
 - Feet feel swollen
- Allodynia

Pressure Palsies /Entrapment Syndrome

- Medial Nerve compression
 - Carpal tunnel syndrome
 - Paraesthesiae
 - Numbness
 - Radiating up forearm or higher
 - Confirmed with nerve conduction studies
- Ulnar Nerve compression
- Lateral popliteal nerve compression
 - Causes foot drop



Assessment

History

1. Most troublesome symptom?
2. Is the pain neuropathic?
3. What is dominant unpleasant symptom?
4. When are the symptoms worse?
5. Fears or beliefs about pain?

Exam

- Neurological
- Vascular
- Blood Pressure
- Urinary albumin excretion

Signs of Neuropathy

- Allodynia
 - Painful response to thermal testing
 - Painful response to cotton sensory testing
- Hyperalgesia
 - Exaggerated response to pinprick sensory test
- Autonomic
 - One limb cooler than other
 - Spontaneous sweating of skin area
 - Abnormal hair/nail growth
 - Blotchy skin

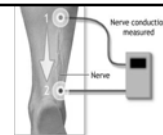
- Absent or reduced ankle reflexes
- Unsteadiness
- Deep tendon reflexes reduced or absent
- Muscle wasting
- Symmetrical stocking like distribution of sensory abnormalities

Diagnostic Studies

- Electromyography (EMG)/Nerve conduction studies (NCV)
 - Negative study does not rule out neuropathic mechanisms
- Quantitative sensory testing
 - Assesses function of small fibers involved in neuropathic pain
- Epidermal skin biopsy
- Functional magnetic resonance testing (fMRI)

Diagnostic Studies

- Nerve conduction studies
 - Checks transmission of electrical current through a nerve (arms/legs)
 - Nerve image is projected onto a screen.
 - Nerve impulses that seem slower or weaker than usual indicate possible damage.
- Electromyography (EMG)
 - Shows how well muscles respond to electrical signals transmitted by nearby nerves.
 - Electrical activity of the muscle is displayed on a screen.
 - A response that is slower or weaker than usual suggests damage to the nerve or muscle.
 - Often done at the same time as nerve conduction studies.



Diagnosing

- A minimum of two abnormalities
 - Symptoms (NSS)
 - Signs
 - Nerve conduction abnormalities
 - Quantitative sensory tests or quantitative autonomic tests

Treatment

Primary Prevention

- Glycemic/metabolic control
- Foot care education

Treatment

- Glycemic/metabolic control
- Pain control
- Reverse neuropathic damage

Pharmacotherapy

- Over-the-Counter analgesics, topicals, supplements
- Antidepressants
- Anticonvulsants
- Opioids

Mechanisms of Action

- Anticonvulsants
 - Na-channel blockers
 - Ca-channel blockers
- Antidepressants
 - Inhibit reuptake of norepinephrine and serotonin
- Opioids
 - Block neurotransmitter release by nociceptor fibers, thus decreasing transmission of pain-inducing signals
- Topical analgesics
 - Na-channel blockade
 - Vanilloid receptor

Over-the-counter Remedies

- Aspirin and Other NSAIDs
- Acetaminophen
- Capsaicin
- A-Lipoic acid (thioctic acid)
- Role in Therapy
 - Breakthrough Pain
 - Accurate History

Capsaicin



- Neuropathic pain-states studied include: diabetic neuropathy, postherpetic neuralgia
- Small unmyelinated C-fiber damage gives rise to burning, lancinating pain, hyperalgesia and dysesthesia
- Efficacy demonstrated in some studies but limited by adverse effects and compliance
- New formulations being studied

A-Lipoic acid

- Effective in randomized clinical trials (studies ongoing)
- Reduces oxygen free radicals
- Improves neuropathic deficits and symptoms
- Orally 1,200-1,800 mg daily
- <http://www.pdrhealth.com/drugs/altmed/alt-med-a-z.aspx>

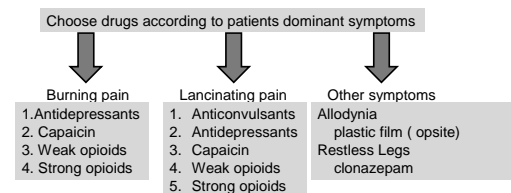
Pharmacologic Management of Neuropathic Pain

- Aim for monotherapy but rational polypharmacy may be necessary
- If using more than one medication- titrate one at a time whenever possible
- Treatment result: significant pain relief and tolerable side effects
- Recognize that there may be significant dose/response variability among patients

FDA-approved Treatments for Neuropathic Pain

- Carbamazepine (Tegretol®, Carbatrol®)
 - Trigeminal neuralgia
- Duloxetine (Cymbalta®)
 - Peripheral diabetic neuropathy
- Gabapentin (Neurontin®)
 - Postherpetic neuralgia
- Lidocaine Patch 5%
 - Postherpetic neuralgia
- Epidurally administered clonidine
- Pregablin (Lyrica®)
 - Peripheral diabetic neuropathy
 - Postherpetic neuralgia

Drug Treatment of Neuropathic Pain



Anticonvulsants

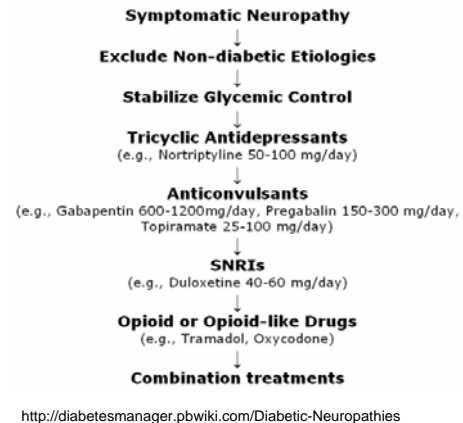
- Carbamazepine (Tegretol®, Carbatrol®)
- Gabapentin (Neurontin®)
- Pregablin (Lyrica®)
- Lamotrigine (Lamictal®)
- Topiramate (Topamax®)

Antidepressants

NRI	SSRI	SNRI
Amitriptyline	Fluoxetine	Duloxetine
Desipramine	Paroxetine	Venlafaxine
Nortriptyline	Sertraline	
	Citalopram	

Opioids

- Tramadol- weak opioid
- Morphine, Oxycodone HCL



Non-Pharmacologic Treatments

- Surgery
- Alternative Therapy
 - Biofeedback
 - Relaxation therapy, meditation
 - Massage therapy
 - Acupuncture
 - B-complex vitamins
- Physical and occupational therapy
- Transcutaneous electrical nerve stimulation
- Psychological support

Showing promise- pathogenetically oriented

- α Lipoic acid- infusion and oral treatment
 - Reduces oxygen free radicals, effective in randomized clinical trials
- C-Peptide
 - Increases nerve blood flow
 - Effective in phase II trials
- Ranirestat- aldose reductase inhibitor
 - Reduces nerve sorbitol
 - Effective in phase II trial

http://care.diabetesjournals.org/cgi/content/full/31/Supplement_2/S255/T1

Treatment Tips

- Each symptom of neuropathic pain may correspond to a distinct mechanism and may only respond to a specific treatment
- Treatment goals should include significant pain relief with tolerable side effects
- Multidisciplinary treatment of chronic pain can be beneficial in managing pain with both pharmacological and non-pharm strategies

Screening Recommendation

- Type 2: At diagnosis and annually thereafter
- Type 1: 5 years after diagnosis and annually thereafter

Why Screen for Neuropathy?

- DPN is asymptomatic in up to 50% of cases
- Annual risk of foot ulceration is 5-7% in DPN cases (<1% in non-neuropathic patients)
- It is common: up to 50% of older type 2 patients
- Most painful symptoms are treatable

1. Boulton AJM, et al. *Diabetes Care*. 2004;27:1458-1486.

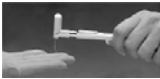
Screening Methods

- Examination (feet should be examined at every visit)
- Ankle reflexes
- One of the following for sensory exam
 - Pinprick
 - Temperature
 - Vibration perception (tuning fork)
 - Pressure perception (10-g monofilament)



Screening

- Comprehensive foot exam
 - *Skin*: color, temperature, deformities/lesions
 - *Structure*: lift toes >15° & heel >45°; check gait & deformities
 - *Vascular*: pulses, edema
 - *Neurosensory* : check reflexes and vibration (more sensitive than touch pressure); **Monofilament testing**
 - Loss of protective sensation increases risk for developing foot sores that may not heal properly.



Prevention

- BG Control.
 - Fasting: 90-130 mg/dl
 - 2 hours post meal: < 140-180 mg/dl
 - A1C: < 7%
- Be active
- Foot Care
- Be smoke free
- Limit alcohol
- Metabolic Control
 - BP ≤ 130/90
 - LDL <100mg/dl; HDL ≥50mg/dl; TG <150mg/dl

Summary

- Educate
 - Prevention
 - Blood Glucose/metabolic control
 - Foot care
- Screen
- Assess, examine feet every visit
- Be Alert for signs
- Monitor response to treatment
- Provide support

Summary

- Diabetic neuropathies are common but not frequently recognized nor treated
- Management can be complex
- A thorough history and detailed exam are essential for diagnosis
- Simple tests can be done in the office
- Treatment should be based on underlying pathological process, predominant symptoms
- New therapies hold promise
- Education is the key to prevention

Thank You

TIPDON
Northern Michigan's Diabetes
Outreach Network
800-847-3665
www.diabetesinmichigan.org

61
09-07

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