Polyneuropathy: My feet are killing me

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• **Polyneuropathy**
  – generalized, homogeneous process
  – affects many peripheral nerves
  – distal nerves affected most

• **Peripheral neuropathy**
  – often used synonymously
  – any disorder of the peripheral nervous system
  – radiculopathies and mononeuropathies

• **Neuropathy**
  – used synonymously with peripheral neuropathy
  – and/or polyneuropathy
  – more generally refers to disorders of the central and peripheral nervous system
Epidemiology of Polyneuropathy

- Data limited
- Variable severity, etiology and pathology
- Multiple assumptions
- Restrictive definitions
Italian epidemiology study, 1995

• 4200 pts ≥ 55yrs, screened by PCP, confirmed by neurologist
• Prevalence of Polyneuropathy
  – 2%; no known risk factors
  – 12%; one risk factor
  – 17%; two risk factors
• Risk factors
  – diabetes mellitus present in 44%
  – alcoholism,
  – non-alcoholic liver disease
  – malignancy
Finnish Diabetes Natural History Study, 1995: Prevalence of polyneuropathy*

- Baseline
  - 8% in diabetics
  - 2% in controls

- At 10 years
  - 42% in diabetics
  - 6% in controls

* Confirmed by NCS
Defining Characteristics

• Axonal (degenerative) vs. demyelinating
• Chronic vs. acute
• Sensory vs. motor
• Autonomic vs. sensorimotor
Etiology

- Diabetic
- Other Systemic
- Autoimmune
- Toxic
- Hereditary
- Environmental
- Idiopathic
Diabetic neuropathy

• Mechanism extremely complex
  – predominantly axonal
  – variable degrees of demyelination
  – inflammatory effects
  – metabolic effects
  – ischemic effects
Other systemic diseases

• Predominantly axonal

• Common
  – Critical Illness (severe sepsis)
  – Carcinoma (late)
Other systemic diseases: Less Common

• Vitamin B12 deficiency
  – Malabsorption vs inadequate intake
  – Slow (years)
  – Risk factors
    • Bariatric surgery
    • Metformin
    • Proton Pump Inhibitors
    • Crohn’s Disease
    • Strict vegetarian diet
Less common, continued

- Other vitamin deficiencies
- Uremia
- Chronic liver disease
- Malabsorption (e.g., Celiac disease)
- Carcinoma
- Lyme disease (rare in Oregon)
- HIV infection
- Multiple myeloma
- Lymphoma
- Benign monoclonal gammopathy (IgA, IgG, IgM)
Other systemic disease: Rare

- Hypothyroidism
- Chronic obstructive lung disease
- Porphyria
- Hypoglycemia
- Primary biliary cirrhosis
- Primary systemic amyloidosis
- Polycythemia vera
- Cryoglobulinemia
- Acromegaly
- Carcinoma (sensory)
Autoimmune

- Predominantly demyelinating
- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Collagen Vascular Diseases
  - SLE
  - Rheumatoid Arthritis
  - Sjogren’s
  - Scleroderma
Toxic - Drugs

- Amiodarone
- Aurothioglucose (gold thioglucone)
- Cisplatin
- Dapsone
- Disulfirn
- Hydralazine
- Isoniazid
- Leflunomide
- Linezolid
- Metronidazole
Toxic – Drugs, cont.

• Misonidazole
• Nitrofurantoin
• Nucleoside analogues (ddC, ddl, d4T)
• Oxaliplatin
• Phenytoin
• Pyridoxine (vit B6)
• Statins??
• Suramin
• Taxol
• Vincristine
Toxins

- Acrylamide
- Alcohol
- Diptheria toxin
- Gamma-Diketone hexacarbons (solvents, lacquers)
- Inorganic Lead
- Organophosphates (insecticides, herbicides, solvents, plasticizers, gear oil, cutting fluid)
- Thallium
Hereditary

- Largely demyelinating
- Charcot-Marie-Tooth
- Hereditary amyloid polyneuropathies
- Hereditary sensory neuropathy
- Porphyric neuropathy
- Fabry disease
- Adrenomyeloneuropathy
- Refsum’s disease
Hereditary, cont

- Ataxia telangiectasia
- Abetalipoproteinemia
- Giant axonal neuropathy
- Friedrich’s ataxia
- Krabbe’s disease
- Mitochondrial disorders
Environmental

- Generally axonal
- vibration-induced
- prolonged cold exposure
- hypoxemia
Idiopathic

- Up to ¼ of patients with polyneuropathy
- Primarily axonal
- Proposed mechanisms
  - impaired glucose tolerance
  - hypertension
  - dyslipidemia
  - increased oxidative stress
Pathologic process in sensory neuropathy

- Change in the microvasculature
- Neuronal dysfunction correlates closely with the development of vascular abnormalities
  - Capillary basement membrane thickening
  - Endothelial hyperplasia
Common Clinical Presentation

- Chronic axonal polyneuropathies most common
  - Injury related to axon length
  - Longer axons affected first
  - Sensory precedes motor symptoms
  - Stocking and glove distribution
  - Symmetrical
  - Progressive
  - Feet, legs, fingers, hands, arms
  - Can progress into the central part of the body
Less Common Presentation Polyneuropathy

- Acute demyelinating (GBS)
- Weakness then sensory loss

- Chronic inflammatory demyelinating
- Simultaneous weakness and gen. sensory loss

- Hereditary
- Slow, insidious numbness
Sensory loss and dysesthesias

• Pain
  – allodynia (light touch, temperature)
  – shooting, stabbing, sharp
  – aching
• Burning
• Numbness
• Tingling
Difficult for pts to articulate

- “My feet feel swollen but look normal”
- “I feel like there is gravel in my shoes”
- “I think my feet are going to explode”
- “Feels like someone peeled the skin off my toes”
- “I thought I was stabbed with an ice pick”
- “Like hot-flashes in my feet”
- “Feels like I am wearing 5 pairs of socks”
Functional Effects

- Abnormal gait/ poor balance – fall risk
- Risk for injury – eg. stepping on sharp objects
- Risk for serious infection
- Reduced activity
- Poor sleep
- Depression/ Anxiety
- Drug/Alcohol abuse
Evaluation

• History
• Pattern of symptom distribution
• Progression
• Think of risk factors
  – recent viral illnesses
  – other systemic symptoms
  – new medications
  – exposures to solvents, heavy metals, other toxins
  – alcohol use
  – family history of neurologic disease
Physical Exam

• Neurologic exam
  – Strength
  – DTRs
    • ankle reflexes may be diminished normally ≥65 years old
  – Gait
  – Balance
  – Pinprick
  – Vibration
  – Proprioception
Exam

• Signs of vascular disease
  – Skin color
  – Skin temperature
  – Edema
  – Hair growth

• Musculoskeletal
  – Charcot Foot
  – Bunions
Differential Diagnosis for Polyneuropathy

• Only straightforward dx – pt with long-standing diabetes mellitus with classic "stocking-glove" sensory loss

• Difficult to distinguish from central nervous system disease
  – spinal cord process
  – acute myopathy
  – neuromuscular junction disease
  – central process
Ddx: Lower Extremity Nerve Dysfunction

• Compression – most common problem
  – Leads to Demyelination
    • Herniated disc
    • Tarsal tunnel
    • Peroneal nerve
    • Orthopedic surgery

• Transection
  • Saphenous vein harvesting
Ddx:

• Nerve ischemia/infarct
  – Vasculitis
  – Atherosclerotic disease
  – Diabetic amyotrophy
• Radiation-induced injury
  – Effects may be delayed years
• Orthopedic
“I think I have neuropathy”

- Lumbosacral radiculopathy
- Tarsal Tunnel Syndrome
- Plantar fasciitis
- Bunions
- Rapidly progressing weakness, numbness
Diagnostic Criteria for Polyneuropathy

• Developed primarily for research purposes but still useful to clinician

• Developed by
  – American Academy of Neurology
  – American Association of Neuromuscular and Electrodiagnostic Medicine
  – American Academy of Physical Medicine and Rehabilitation
Diagnostic Criteria

• Symptoms alone have poor diagnostic accuracy
• Multiple neuropathic symptoms are more accurate than single symptoms
  – Pain, Burning, Numbness, Tingling
• Signs are better predictors than symptoms
• Single abnormality on exam less sensitive than multiple abnormalities
• Exam should look for combination of signs
  – Diminished or absent ankle reflexes*
  – Diminished distal sensation
  – Distal muscle weakness or atrophy
• Abnormal EDS provides higher specificity
• EDS should not be used alone to make diagnosis
Diagnostic Evaluation

- Electrodiagnostic Studies (EDS)
- Laboratory Testing
- Biopsy
- Autonomic testing
- Quantitative sensory testing
- Imaging
Electrodiagnostic studies (EDS)

- Electromyography (EMG)
- Nerve conduction studies (NCS)
- Referrals for studies vs. referral to neurology
  - provide background information
  - avoid narrowing the question too much
EDS findings

• Neuropathy vs. myopathy (EMG)
• Polyneuropathy vs. other peripheral nerve disorder (eg lumbar stenosis)
• Axonal vs demyelinating (decreased signal amplitude vs. decreased velocity)
Limitations of EDS

- **Cannot effectively assess small fiber dysfunction**
  - Superimposed processes limits accuracy
  - Lumbar radiculopathy in a diabetic patient
  - Velocity will slow and amplitude increase if the patient's limbs are cool
  - Normal values not firmly established in older populations
  - Obesity makes certain tests difficult to perform
Limitations of EDS, cont

• EMG/NCS is uncomfortable!
  – Patients unwilling/unable to complete study
• Results are operator dependant
  – Training & experience important

• **Bottom Line**
• EDS rarely beneficial in the absence of motor symptoms
Laboratory testing

• selective use
  – history and the results of EDS
  – more cost-effective, less confusing

• if classic symptoms and no EDS, best tests are:
  – blood glucose
  – serum B12 level with MMA (w/wo homocysteine)
  – serum protein electrophoresis
Lab Testing if EDS = Axonal

- Serum glucose
- Serum protein electrophoresis
- Vitamin B12 level
- Anti-nuclear antibody
- Erythrocyte sedimentation rate
- Rapid plasma reagin (RPR)
- Glycohemoglobin
Additional Labs for EDS = Axonal Considering History

- HIV serology
- Urine/blood for heavy metals
- Urine/blood for porphyrins
- Rheumatoid factor
- Sjögren's syndrome testing (Anti-Ro, Anti-La Antibodies)
- Lyme testing
- Vitamin B1 (thiamine) erythrocyte transketolase activation assay or whole blood level
- Methylmalonic acid and homocysteine levels (in patients with borderline low serum B12 levels)
- Hepatitis screen (for types B and C)
Lab Testing if EDS = Demyelinating

- Serum protein electrophoresis
- Immunoelectrophoresis
- Urine protein electrophoresis
- Hepatitis screen (for types B and C)
- Lumbar puncture
Additional Labs for EDS = Demyelinating Considering History

- Antimyelin associated glycoprotein (MAG) testing (in patients with predominantly sensory symptoms)
- Anti-GM1 test (in patients with predominantly motor symptoms)
- HIV
- Genetic testing for Charcot-Marie-Tooth Disease; generally, the electrophysiology is also suggestive of a hereditary condition
Nerve Biopsy (Sural)

• Reserved for
  – difficulty defining axonal vs. demyelinating
  – asymmetry or focality of symptoms

• Can identify
  – infiltrative diseases (eg. amyloid neuropathy)
  – infectious diseases (eg. Leprosy)
  – inflammatory neuropathies (eg. chronic inflammatory demyelinating polyneuropathy, mononeuropathy multiplex due to vasculitis, sarcoidosis)
Skin Biopsy

• Helpful in small fiber neuropathy
  – Distal P,B,N,T with normal EDS
  – Unmyelinated fibers
• Epidermal tissue just proximal to ankle
• Intraepidermal nerve fiber density compared with age-dependent normal values
• May be useful in following disease progression or response to treatment
Autonomic testing

• Can help support diagnosis of small fiber sensory neuropathy
• Composite autonomic scoring scale
  – orthostatic blood pressure
  – quantitative sudomotor axon reflex test
  – heart rate response to tilt
  – heart rate variability with deep breathing
  – changes in blood pressure with Valsalva
Quantitative sensory testing

• Measure degree of sensory loss
  – Temperature
  – Vibration
• Identify subtle abnormalities
• Demonstrate the progression or stability of disease
Imaging – Back pain

• Plain films of spine
  – nonfocal, nonradiating back pain w/o sig. neuro compromise

• MRI
  – Standard evaluation for lumbosacral spine disease
  – Consider in idiopathic plexopathies (?mass lesion)
  – Comparison of MRI and EMG in diagnosis of radiculopathy found only 60% agreement
Everyone still awake?
Management

- Treatment of the underlying disease
- Alleviation of symptoms
- Prevention of complication
Treatment of underlying process

• Axonal Polyneuropathy
  – Reduce exposure – Examples:
    • Stop drinking
    • Tight glucose control
    • Thyroid replacement
    • Treatment of underlying rheumatologic disease

• Demyelinating Polyneuropathy
  – intravenous immune globulin (IVIG)
  – glucocorticoids
  – plasma exchange
Treatment of symptoms

• Drugs – Pain only
  – Antidepressants
  – Anticonvulsants
  – Analgesics
  – Other

• Electrical Nerve Stimulation (TENS)

• Combination Electrochemical Treatment
Antidepressants

• Tricyclics – contraindicated in cardiac disease
  – Amitriptyline
  – Nortriptyline (fewer anticholinergic side effects)
  – Desipramine

• SNRIs
  – Duloxetine (Cymbalta)
  – Venlafaxine (Effexor)
Anticonvulants

- Pregabalin (Lyrica) – approved for diabetic neuropathy
- Gabapentin
- Valproate
- Carbamazepine
Analgesics

- NSAIDs
- Opioid and opioid-like drugs
- problems with long term use
  - Tramadol
  - Dextromethorphan
  - Oxycodone
  - Morphine
- Topical
  - Capsaicin
  - Lidocaine patch
Drugs: Other

- Alpha-lipoic acid 600 mg qd
- Isosorbide dinitrate topical spray
- Mexiletine (Mexitil)
  - Same class as lidocaine, available as a pill
- Acetyl-L-carnitine
- Baclofen
Prevention of complications

• Meticulous foot care
• Careful wound treatment
• Balance training/physical therapy
• Orthopedic shoes
• Ankle-Foot Orthotics (AFOs)
Other Treatments

• TENS
• Combination Electrochemical Treatment (CET)
  – Advanced form electrical stimulation technology
  – Local anesthetic placed around the nerve roots of the ankle
  – Infrared light therapy to improve circulation
  – Improvement in numbness as well as pain
A New Approach to Management of Neuropathy with Electrical Current and Local Anesthetic
• Series of combined electrochemical treatments (CET) twice a week for 12 weeks
  – “Ankle block” using Bupivicaine 0.25-0.5% (8-10ml per ankle)
  – The TENS device delivers both amplitude modulation (AM) and frequency modulated (FM) output in the low frequencies (<2,000Hz) and medium frequencies (2,000-100,000Hz)
• Greater depth of penetration through the dermal tissue compared to standard TENS
• Affects voltage-gated channels and receptors within target tissue
• net effect is hypothesized to result in analgesia, improved circulation, muscle activation, training and strengthening
• underlying physiologic response is not fully understood, but is thought to involve improved second-messenger formation (cyclic AMP) mediated membrane repair processes
• Not widely studied
  – First developed ~10 years ago
• Largest study
  – out of Wisconsin
  – Team included neurologist and podiatrist
  – Drs. Cernak, Marriott, Martini and Fleischmann
Cernak, et al

- 5/2008-7/2010
- 101 patients
- 5.39 = avg. pretreatment pain score (0-10)
- 0.98 = avg posttreatment pain score
- 81.8% reduction
- Long terms results (greater than 2 years) have not been assessed
- Pre and post NCS of motor and sensory nerves (subset of pts) with mixed results
References


2. Cernak, Marriott, Martini, Fleischmann, Silvani, McDermott, Electric current and local anesthetic combination successfully treats pain associated with diabetic neuropathy. Practical pain management, April 2012


Links

Thanks!