VASCULAR vs NEUROPATHIC PAIN: DIFFERENTIAL DIAGNOSIS

ALLEN MARK JACOBS DPM, FACFAS
CONSIDERATIONS

• VASCULAR PAIN
  – SECONDARY TO LOSS OF BLOOD FLOW
    • ISCHEMIA
    • VASCULITIS
    • VASOSPASM
    • COMPRESSION

• NEUROPATHIC PAIN
  – DIABETIC NEUROPATHY
  – ENTRAPEMENT
  – NEUROPATHY
    • TARSAL TUNNEL SYNDROME
    • SPINAL COMPRESSION SYNDROME
PRACTICAL CONSIDERATIONS

• NEUROPATHY AND VASCULAR DISEASE MAY CO-EXIST IN THE SAME PATIENT

• THE SYMPTOMS OF NEUROPATHY AND VASCULAR DISEASE MAY BE SIMILAR
  – NOCTURNAL PAIN
  – CRAMPING/PAIN WITH AMBULATION

• BOTH NEUROPATHY AND VASCULAR DISEASE MAY EXIST WITH INITIAL MINIMAL SYMPTOMATOLOGY
<table>
<thead>
<tr>
<th>COMMON RISK FACTORS FOR NEUROPATHY AND PAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HYPERTENSION</td>
</tr>
<tr>
<td>• CHOLESTEROL</td>
</tr>
<tr>
<td>• AGE</td>
</tr>
<tr>
<td>• DIABETES</td>
</tr>
<tr>
<td>• TOBACCO</td>
</tr>
<tr>
<td>• HOMOCYSTEINE</td>
</tr>
</tbody>
</table>
DIABETIC NEUROPATHY AND ISCHEMIA

Hyperglycemia

Endoneural Ischemia

Impaired Neuronal Regeneration

Neuronal Injury

OXIDATIVE STRESS
NERVE PERFUSION INJURY

Progressive Diabetic Peripheral Neuropathy
Examination of tissues from patients with diabetes reveals capillary damage, including occlusion in the vasa nervorum. Reduced blood supply to the neural tissue results in impairments in nerve signaling that affect both sensory and motor function.

PRACTICAL CONSIDERATIONS

• ENTRAPEMENT NEUROPATHIES ARE MORE COMMON IN DIABETES MELLITUS
• OCCURS IN 1/3 OF PATIENTS WITH DM
  – COMMON PERONEAL NERVE
  – TARSAL TUNNEL
  – LATERAL FEMORAL CUTANEOUS
• ACUTE MONONEURITIS
• EFFECTS OF CO-MORBID CONDITIONS
• EFFECTS OF MEDICATIONS
DIABETIC NEUROPATHY

- 66% PATIENTS WITH DM
- 80% DPN
- 50% SYMPTOMATIC
- 10-30% ANTINOCICEPTIVE TX

CHEN H, LAMER TH, RHO RH ET AL. MAYO CLIN PROCEED. 79; 2004
BOULTON AJM. CLIN. DIAB. 23, 2005
BOULTON AJM, MAILIK RA, AREZZO JC, SOSENKO JM. DIAB. CARE 27, 2004
### Symptoms and Signs of Diabetic Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Small Fiber</strong></td>
<td></td>
</tr>
<tr>
<td>Numbness or loss of feeling (asleep or “bunched up sock under toes” sensation)</td>
<td>Diminished vibratory perception</td>
</tr>
<tr>
<td>Prickling/Tingling</td>
<td>Decreased knee and ankle reflexes</td>
</tr>
<tr>
<td><strong>Aching Pain</strong></td>
<td>Reduced protective sensation such as pressure, hot and cold, pain</td>
</tr>
<tr>
<td><strong>Burning Pain</strong></td>
<td>Diminished ability to sense position of toes and feet</td>
</tr>
<tr>
<td><strong>Lancinating Pain</strong></td>
<td>Pain is deep, aching or cramping</td>
</tr>
<tr>
<td><strong>Allodynia</strong></td>
<td></td>
</tr>
<tr>
<td>Defective Thermal Sensation</td>
<td></td>
</tr>
<tr>
<td>Decreased Sweating</td>
<td></td>
</tr>
<tr>
<td><strong>Large Fiber</strong></td>
<td></td>
</tr>
</tbody>
</table>

Symptoms and signs progress from distal to proximal over time.

CLAUDICATION

• CLAUDICATION
• “MUSCLE CRAMPING”
• PSEUDOCLAUDICATION
  – LUMBAR SPINAL STENOSIS
  – DISC HERNIATION
  – OSTEOPOROSIS
  – NEOPLASM
LEG CRAMPING: COMMON CAUSES

• FATIGUE
• HYPONATREMIA
• HYPOKALEMIA
• DEHYDRATION
• HYPOMAGNESEMIA
• HYPOCALEMIA
PSEUDOCLAUDICATION
(NEUROGENIC CLAUDICATION)

- LOW BACK PAIN AND EXTREMITY PAIN
- 12% COMMUNITY DWELLING MEN
- 21% RETIREMENT COMMUNITIES
- PAIN
- WEAKNESS
- TINGLING
- FATIGUE
- HEAVINESS
- COMMONLY BILATERAL

ENGLUND, J.CURR SPORTS MED REP 6 (1) 2007
NEUROGENIC CLAUDICATION

• SITTING RELIEVES SYMPTOMS
  – VS STANDING

• WALKING UPHILL BETTER TOLERATED
  – VS DOWNHILL

• EXERCISE ON A STATIONARY BIKE IN SEATED, FLEXED POSITION BETTER TOLERATED

• MAY HAVE RADICULAR CHARACTERISTICS

GENEVA, S., ATLAS, S.J., BEST MED PRACT RES CLIN RHEUM 24 (2) 2010
NEUROGENIC CLAUDICATION

• DEGENERATIVE SPONDYLOLISTHESIS
• ANKYLOSING SPONDYLITIS
• RADIOGRAPHHS
• MRI/CT
## Clinical Spectrum of Claudication

<table>
<thead>
<tr>
<th>Intermittent (Atherosclerosis)</th>
<th>Neurogenic (Lumbar Spinal Stenosis)</th>
<th>Venous (Deep Vein Thrombosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pain is in the muscle of the calf, thigh or buttock</td>
<td>• Pain is in whole leg can be associated with tingling and numbness</td>
<td>• Involvement of whole leg.</td>
</tr>
<tr>
<td>• Unilateral in femoropopliteal disease</td>
<td>• Bilateral (Can also be less commonly unilateral)</td>
<td>• Pt may describe feeling their &quot;leg is going to burst&quot;</td>
</tr>
<tr>
<td>• Bilateral in aorto-iliac disease</td>
<td>• Comes on suddenly on standing up or walking</td>
<td>• Most commonly unilateral</td>
</tr>
<tr>
<td>• Gradual onset after walking &quot;claudication distance&quot;</td>
<td>• Relieved by sitting down, bending over and stopping walking</td>
<td>• Gradual onset after beginning to walk</td>
</tr>
<tr>
<td>• Pain is relieved by rest</td>
<td>• Unable to straighten legs</td>
<td>• Relief on elevating the leg</td>
</tr>
<tr>
<td>• Absent/reduced pulses</td>
<td></td>
<td>• Cyanosed</td>
</tr>
</tbody>
</table>

NB. The Claudication distance is a constant distance the patient was able to walk before the onset of symptoms.
REST PAIN

• NOCTURNAL EXACERBATION FREQUENT WITH NEUROPATHY
• RESTLESS LEG SYNDROME
• NOCTURNAL MUSCLE CRAMPING
NIH CRITERIA
RLS/WILLIS-EKBOM DISEASE

• URGE TO MOVE THE LIMB
• RELIEF WITH MOTION
• WORSENING AT REST
• WORSENING AT NIGHT
THE JIMMY LEG

1. A JERKING MOTION WITH ONES LEG WHILE SLEEPING
2. MAY CAUSE RELATIONSHIP PROBLEMS AND NOT ALLOW A PERSON TO SLEEP WITH ONES PARTNER
3. “YEAH, BECAUSE SHE’S THROWING OFF MY WHOLE SLEEP. SHE’S GOT THE JIMMY LEGS”
DOPAMINE AGONISTS

• ROPINIROLE (REQUIP)
• PRAMIPEXOLE (MIRAPEX)
• ROTIGOTINE (NEUPRO)
OTHER COMMON CAUSES

- VENOUS INSUFFICIENCY
- ARTERIAL INSUFFICIENCY
- RENAL DISEASE
- THYROID DISEASE
- PREGNANCY
- DIABETES
- HYPOGLYCEMIA
  - REACTIVE HYPOGLYCEMIA
- HYPERINSULINEMIA
OTHER CONSIDERATIONS

• PRIMARY NEUROLOGIC DISORDERS
  – EG-MULTIPLE SCLEROSIS
  – STIFF PERSON SYNDROME

• DIABETIC MOTOR NEUROPATY

• PRIMARY MYOPATHIES
NOCTURNAL LEG CRAMPING

• TYPICALLY CALVES AND SOLES
• SORENESS MAY REMAIN
• MORE COMMON IN OLDER PATIENTS
• ETIOLOGY:
  – DEHYDRATION
  – LOW MAGNESIUM
  – LOW POTASSIUM
  – LOW CALCIUM
  – LOW SODIUM
  – REDUCED BLOOD FLOW
  – LACTIC ACID BUILD UP FROM EXERCISE
  – LATE IN PREGNANCY
CRAMPING: EFFECTS OF MEDICATIONS

- DIURETICS
- STATINS
  - 80% OF ATHLETES USING STATINS
  - 25% OF STATIN USING PATIENTS
  - COENZYME Q10 HELPFUL
- LONG ACTING ADRENERGIC BETA-AGONISTS
  - USED TO TREAT ASHMA, COPD
    - SALMETEROL (EG-ADV AIR (FLUTIASONE/SALMETEROL)
    - FORMOTEROL (EG-FORADIL, OXEZE, ATOCK)
    - BAM BUTEROL (EG-BAM BEC, OXEOL)
PAD CRAMPING

- **PENTOXIFYLLINE**
  - TRENTAL, ARTAL, PENTILIN, PENTOXIN
  - 400mg TID

- **CILOSTAZOL**
  - PLETAL
  - 100 mg BID
NAFTIDROFURYL

- VASODILATOR
- ANTAGONIST TO HT-2 RECEPTORS IN SMOOTH MUSCLE
- USEFUL WITH PAD CRAMPING
- NAFTIDROFURYL (VASCUPRAX) CAPSULES
- 100mg TID
- LIVER METABOLISM, RENAL EXCRETION
EVALUATION OF NEUROPATHY

- HISTORY
- EXAMINATION
- EMG/NCV
- QUANTITATIVE SUDOMOTOR AXON REFLEX TESTING (QSTART)
- PSSD
- NEUROMETER
- NEUROPAD
- IENFD
NEURODIAGNOSTIC STUDIES

• HISTORY AND NEUROLOGIC EXAMINATION
  – DIFFERENTIAL DIAGNOSIS

• SELECT APPROPRIATE TESTING
  – SENSORY, MOTOR CONDUCTION
  – EMG
  – QUANTITATIVE SENSORY TESTING
  – AUTONOMIC REFLEX TESTING
  – IENFD
NEUROPATHY SCREENING

- 128-Hz TUNING FORK*
- PIN PRICK
- 10 GRAM FILAMENT*
- ANKLE REFLEXES
- > 87% SENSITIVITY

PREDICTIVE OF FOOT ULCERATION

PHARMACOLOGIC THERAPY

• ANALGESIC
  – ANTIDEPRESSANTS
  – ANTICONVULSANTS
  – OPIOIDS

• REMITTIVE
  – CONTROL OF DM
  – ALPHA-LIPOIC ACID
  – CARNITINE
  – L-METHYLFOLATE, B6, B12
## Diabetic Neuropathy: Current Treatments

- **25%** NO TREATMENT
- **53.9%** OPIOIDS
- **39.7%** NSAIDS
- **21.1%** SSRI’S
- **11.3%** TCI’S
- **11.1%** ANTICONVULSANTS

Berger A, Dukes EM, Oster J. Pain 2004; 5
TREATMENT PROTOCOLS

- TOPICAL LIDOCAINE
- SECONDARY AMINE TRICYCLIC ANTIDEPRESSANTS
- SERATONIN AND NOREPINEPHRINE DUAL UPTAKE INHIBITORS
- CALCIUM CHANNEL $\alpha_2$-$\delta$ LIGANDS
- TRAMADOL
- OPIOID ANTAGAGONISTS
- HIGH CONCENTRATION CAPSAICIN PATCH

- De Leon-Casasola, O. 2011 *Pain Medicine* 12
  (SUPPL. 3), pp. S100-S108
PDN TREATMENT RESULTS

- 14 PATIENTS
- ALL STARTED ON DULOXETINE OR PREGABALIN
- 10 MONTH STUDY
- 33% IMPROVED WITH PREGABALIN
- 21% IMPROVED WITH DULOXETINE
- DULOXETINE 38% ADVERSE SIDE EFFECTs

Mittal, M., Pasnoor, M., Mummaneni, R.B., Khan, S., McVey, A., Saperstein, D., Herbelin, L., Barohn, R.J. 2011 *International Journal of Neuroscience* 121 (9), pp. 521-527
PHARMACOLOGIC MANAGEMENT OF DIABETIC NEUROPATHY

- 69 PUBLISHED STUDIES IN LAST 5 YEARS USING MEDLINE AND EMBASE
- 66% INCREASE IN STUDIES
- STUDIED DRUGS: TCA, SNRI, ANTICONVULSANTS, OPIOIDS
- MOST PATIENTS WITH INSUFFICIENT PAIN RELIEF

FINNERUP NB., SINDRUP SH., JENSEN TS. PAIN 150 (3) 2010
TREATMENT

- Fibromyalgia pain treatment
- Duloxetine
- Pain treatment in depressed patients
- Pregabalin treatment for neuropathic pain
- Neuropathic pain
- Opioid misuse
- Opioids for treatment of chronic pain
TOPICAL MANAGEMENT

- KETAMINE 10%
- GABAPENTIN 6%
- CLONIDINE 0.2%
- LIDOCAINE 5%
- IMIPRIMINE 3%
- NIFEDIPINE 2%
- DOXEPIN 5%
EVALUATION OF PVD

MEASURE ABI

INDEX > 1.30
INDEX 0.91 – 1.30
INDEX < 0.90
<table>
<thead>
<tr>
<th>CLINICAL PRESENTATION</th>
<th>ABI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>&gt; .90</td>
</tr>
<tr>
<td>CLAUDICATION</td>
<td>0.5 - .9</td>
</tr>
<tr>
<td>REST PAIN</td>
<td>0.21 – 0.49</td>
</tr>
<tr>
<td>TISSUE LOSS</td>
<td>&lt; 0.2</td>
</tr>
</tbody>
</table>
PAD EVALUATION
### Table 2. Characteristics of Imaging Methods Used to Diagnose Peripheral Arterial Disease.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Duplex Ultrasound</th>
<th>Digital-Subtraction Angiography</th>
<th>Magnetic Resonance Angiography</th>
<th>Computed Tomographic Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Noninvasive, can be used to visualize and quantify severity of lesion</td>
<td>Gold standard, high resolution, can be used to guide intervention.</td>
<td>Noninvasive, no radiation or iodinated contrast material used, three-dimensional</td>
<td>Noninvasive, higher spatial resolution than with magnetic resonance angiography, three-dimensional</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Operator-dependent, imaging limited by dense calcification</td>
<td>Invasive, ionizing radiation and iodinated contrast material used, two-dimensional</td>
<td>Lower spatial resolution than with computed tomographic angiography, contraindicated if patient has claustrophobia, image artifact if stent present</td>
<td>Ionizing radiation (25% of dose with digital-subtraction angiography) and iodinated contrast material used, imaging limited by dense calcification</td>
</tr>
<tr>
<td>Charge (Medicare)*</td>
<td>$252.14</td>
<td>$474.07</td>
<td>$973.75</td>
<td>$530.45</td>
</tr>
</tbody>
</table>

*The charges shown represent the allowable total charge by Medicare in the New Orleans area.*
<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CLINICAL EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>ASYMPTOMATIC</td>
</tr>
<tr>
<td>1</td>
<td>MILD CLAUDICATION</td>
</tr>
<tr>
<td>2</td>
<td>MODERATE CLAUDICATION</td>
</tr>
<tr>
<td>3</td>
<td>SEVERE CLAUDICATION</td>
</tr>
<tr>
<td>4</td>
<td>ISCHEMIC REST PAIN</td>
</tr>
<tr>
<td>5</td>
<td>MINOR TISSUE LOSS</td>
</tr>
<tr>
<td>6</td>
<td>MAJOR TISSUE LOSS</td>
</tr>
<tr>
<td>Recommendations</td>
<td>Class</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Supervised exercise therapy is indicated.</td>
<td>I</td>
</tr>
<tr>
<td>Non-supervised exercise therapy is indicated when supervised exercise therapy is not feasible or available.</td>
<td>I</td>
</tr>
<tr>
<td>In patients with intermittent claudication with symptoms affecting daily life activity, drug therapy may be considered.</td>
<td>IIb</td>
</tr>
<tr>
<td>In the case of intermittent claudication with poor improvement after conservative therapy, revascularization should be considered.</td>
<td>IIa</td>
</tr>
<tr>
<td>In patients with disabling intermittent claudication that impacts their activities of daily living, with culprit lesions located at the aorta/iliac arteries, revascularization (endovascular or surgical) should be considered as first-choice therapeutic option, along with the risk factor management.</td>
<td>IIa</td>
</tr>
<tr>
<td>Stem cell/gene therapy is not indicated.</td>
<td>III</td>
</tr>
</tbody>
</table>

*a*Class of recommendation.  
*b*Level of evidence.  
*c*References.
### Table 3. AHA–ACC Guidelines for Pharmacologic Management of Claudication.*

<table>
<thead>
<tr>
<th>Medication and Class of Evidence</th>
<th>Level of Evidence</th>
<th>Dose</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cilostazol</td>
<td>A</td>
<td>100 mg two times/day</td>
<td>Contraindicated in heart failure; headache, diarrhea, palpitations, dizziness</td>
</tr>
<tr>
<td>Class IIb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>A</td>
<td>400 mg three times/day</td>
<td>Sore throat, dyspepsia, nausea, diarrhea</td>
</tr>
<tr>
<td>Arginine</td>
<td>B</td>
<td>3 g three times/day</td>
<td>Gastrointestinal distress, drop in hematocrit</td>
</tr>
<tr>
<td>Propionyl levocarnitine</td>
<td>B</td>
<td>1–2 g two times/day</td>
<td>None or mild</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>B</td>
<td>120–160 mg/day</td>
<td>None or mild</td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>A</td>
<td>Beraprost: 40 µg three times/day</td>
<td>Headache, flushing gastrointestinal distress</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>C</td>
<td>50 mg/day</td>
<td>None or mild</td>
</tr>
<tr>
<td>Chelation EDTA</td>
<td>A</td>
<td>1.5–3 g intravenously two times/wk</td>
<td>Hypocalcemia, renal failure, proteinuria, gastrointestinal distress</td>
</tr>
</tbody>
</table>

* Information is from the American Heart Association and the American College of Cardiology (Hirsch et al.*). Class I evidence is defined as evidence, general agreement, or both that the treatment is beneficial, useful, and effective; class IIb as conflicting evidence or divergence of opinion about efficacy or usefulness (or efficacy that is less well established by evidence or opinion); and class III as evidence, general agreement, or both that the treatment is not beneficial, useful, and effective. Levels of evidence are classified as follows: level A, data derived from multiple randomized trials or meta-analyses; level B, data derived from a single randomized trial or from nonrandomized studies, and level C, the consensus opinion of experts, data from case studies, or the standard of care.
SUMMARY:
EVALUATION

- HISTORY
- VASCULAR EXAMINATION
  - SCREENING NON-INVASIVE STUDIES
- NEUROLOGIC EXAMINATION
  - ELECTRODIAGNOSTIC STUDIES
- BICYCLE TEST OF VAN GELDEREN
**DIFFERENTIAL DIAGNOSIS**

Table 1. Differentiation of True Claudication from Pseudocludication (Nonvascular Causes).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intermittent Claudication</th>
<th>Spinal Stenosis</th>
<th>Arthritis</th>
<th>Venous Congestion</th>
<th>Compartment Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Character of discomfort</td>
<td>Cramping, tightness, or tiredness</td>
<td>Same symptoms as with claudication or tingling, weakness, or clumsiness</td>
<td>Aching</td>
<td>Tightness, bursting pain</td>
<td>Tightness, bursting pain</td>
</tr>
<tr>
<td>Location of discomfort</td>
<td>Buttock, hip, thigh, calf, foot</td>
<td>Buttock, hip, thigh</td>
<td>Hip, knee</td>
<td>Groin or thigh</td>
<td>Calf</td>
</tr>
<tr>
<td>Exercise-induced discomfort</td>
<td>Yes</td>
<td>Variable</td>
<td>Variable</td>
<td>After walking</td>
<td>After excessive exercise</td>
</tr>
<tr>
<td>Walking distance</td>
<td>Reproducible</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Discomfort with standing</td>
<td>No</td>
<td>Yes</td>
<td>Yes, changes with shift in position</td>
<td>Yes, changes with shift in position</td>
<td>Yes, changes with shift in position</td>
</tr>
<tr>
<td>Relief of discomfort</td>
<td>Rapid relief with rest</td>
<td>Relief with sitting or otherwise changing position</td>
<td>Slow relief with avoidance of bearing weight</td>
<td>Slow relief with leg elevation</td>
<td>Slow relief with leg elevation</td>
</tr>
<tr>
<td>Other</td>
<td>Associated with atherosclerosis and decreased pulses</td>
<td>History of lower-back problems</td>
<td>Discomfort at joint spaces</td>
<td>History of deep venous thrombosis, signs of venous congestion</td>
<td>May occur in athletes after strenuous exercise</td>
</tr>
</tbody>
</table>

* Information is from the American Heart Association and the American College of Cardiology (Hirsch et al.⁹) and from Schmieder and Comerota.¹⁰
SUMMARY

- ALWAYS CONSIDER PAD AS A POTENTIAL ETIOLOGY OF SIGNS/SMPTOMS
- NEUROPATHY AND PAD MAY CO-EXIST
- CONSIDER PRESENCE OF ENTRAPEMENT NEUROPATHY
- CONSIDER OTHER ETIOLOGIES
  - DRUG INDUCED
  - METABOLIC ASSOCIATED