Myalgia: A Painful Diagnosis

John T. Kissel, M.D.
Texas Neurological Society
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Disclosures
- Received support from Alexion for a clinical trial of eculizumab in MG
  ➢ Scientific advisory committee
- Received support from Cytokinetics for a clinical trial in ALS
- Will be discussing some off label uses of drugs and agents
- The only thing harder than giving a talk on myalgia…is seeing patients with it!

Muscle Pain
Epidemiology
- Most common complaint in NM clinics ➢ ~50% of referrals for muscle biopsy
- Prevalence of diffuse myalgia ~10%
  ➢ ~20% prevalence of focal myalgia
- 20-50% complain of muscle tiredness ➢ Up to 25% of primary care OP visits
- 90% of myalgia patients have fatigue ➢ 95% of CFS patients have myalgia

Muscle Pain
Problems for Clinicians
- Pain only symptom in many patients ➢ No signs of disease (e.g. weakness)
  ➢ Difficult to assess at bedside
- Myalgia may arise from many sources ➢ Ortho, rheum, endocrin, gen med, psych
  ➢ May not be related to muscle disease
- Many patients are “undiagnosable” in the usual sense

Diagnoses in Myalgia Patients
Mills and Edwards, 1983

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># Pts.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme defects</td>
<td>16</td>
<td>15%</td>
</tr>
<tr>
<td>Inflammatory myopathy</td>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td>Neurogenic disorders</td>
<td>7</td>
<td>6%</td>
</tr>
<tr>
<td>Endocrine &amp; metabolic</td>
<td>6</td>
<td>6%</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>72</td>
<td>66%</td>
</tr>
<tr>
<td>Total</td>
<td>109</td>
<td>100%</td>
</tr>
</tbody>
</table>

Pre-genetic era!

Filosto et al, Neurology 2007

The role of muscle biopsy in investigating isolated muscle pain
M. Filosto, MD, PhD; P. Torina, MD; G. Vaccarini, MD, PhD; L. Bertolasi, MD; A. Simoni, MD; N. Bizzato, MD; and G. Tonini, MD

- 240 patients presenting with isolated myalgias
  ➢ Excluded statin patients; only 2 FM patients
- Battery of tests done on each biopsy
  ➢ Histochem, biochem, immunohistochemistry
  ➢ No genetic testing
- Correlated findings with CK, EMG, clinical picture
Filosto et al, 2007

- Five groups of biopsies
  - 20% normal
  - 80% abnormal
- BUT
  - Only 20% had diagnosis
  - Only 6% had muscle diagnosis (metabolic)
  - Only 2% with normal strength had diagnosis
    - High CKs (7x normal)
    - Exercise pain only

Filosto et al, Neurology 2007

- Many myalgia patients DO have biopsy abnormalities, but they are usually non-specific
  - They usually do NOT lead to a diagnosis (myth 1!)
- Routine biopsy NOT indicated in patients with isolated myalgia; careful patient selection is needed
- Important info for referring doctors AND patients!

Patients with Myalgia

Objectives

- Present 5-6 cases of patients with “myalgias”
  - Basic approach myalgia patient
  - When to biopsy and when to not!
- Present overview of myalgia in general
  - Terminology & classification
  - Highlight mistakes & myths seen in clinic
- Discuss several conditions that can present with isolated generalized myalgia (i.e. no weakness)
  - Including the “F--- word” (fibromyalgia)

The Patient with Myalgia

Case 1

33 yo WF with 6-9 mos. muscle aches, pain
- Dull, aching soreness in most muscles
- Worse after almost any activity
- Complains of “weakness” during ADLs
- PMH normal; admits to mild depression
  - Missing work as dept store cashier
  - Asking about disability
- Given diagnosis of fibromyalgia

Evaluation of Muscle Pain

- Screening examination
  - Labs. CBC, ESR, TFTs, lyes)
- Neuro. eval - strength, endurance testing
  - Serum CK, electrodiagnostic studies

The Patient with Muscle Pain

General Approach

- Careful history attending to type of pain
  - Consideration of localization/pathogenesis
  - Analysis of disease possibilities
- Exam. with attention to strength testing!
  - Most common mistake we see (& make)!!
  - Judicious lab tests
  - Routine (e.g. CK and EMG)
  - Specialized (FET, biopsy, genetic testing)
Case 1
Laboratory Studies

- 4+/5 SA, HF weakness
- Serum CK normal
- EMG - “minimally myopathic”
- Biopsy - inflammation & necrosis
- Dx. as polymyositis
  - Did well on steroids!
- I violated my own rule!

Myalgia Terminology
Types of Pain

- “I don’t have any pain at all…it just hurts!”
- “Pain” can mean numbness, stiffness, tingling, restlessness, burning, swelling
- Useful to classify 4 types of muscle pain;
  (after Layzer, 1985)
  - Contracts -- Cramps
  - Stiffness -- Aching myalgia

Myalgia Types
Cramp

- Least common myalgia, can be excruciating
- Forceful, sustained contraction
  - Localized hard nodule in muscle
- Electrically silent by EMG!
- Sudden onset with exercise (may be mild)
  - May persist for hours & result in rhabdo.
- Hallmark of glycolytic dx. (eg McArdle’s)
  - FET useful screen for these disorders

Contractures
Differential Diagnosis

Glycolytic enzyme defects
- Phosphorylase deficiency (McArdle’s)
- Phosphofructokinase deficiency
- Phosphoglycerate kinase deficiency
- Phosphoglycerate mutase deficiency
- Debrancher enzyme deficiency
- Lactate dehydrogenase deficiency
- Paramyotonia congenita
- Hypothyroid myopathy with myoedema
- Rippling muscle syndrome
- Brody’s disease

Myalgia Types
Cramp

- HealthSmart Advice from Doctors
- What science knows about muscle cramps

Most muscle cramps are harmless, but they can indicate other problems.

Muscle Cramps
ALS
Cramps
Muscle Differential Diagnosis
- Idiopathic (normal cramps)
- Exertional, post-exertional, nocturnal
- Neurogenic cramps (MND, PN, radics)
- Cramps due to altered neural environment
  - Pregnancy
  - Metabolic disorders (renal or liver failure)
  - Hypothyroidism
  - Adrenal insufficiency
  - Electrolyte disturbances/volume depletion

Myalgia Types
Stiffness
- Non-specific term that refers to tightness
  - Resistance to passive stretch
  - Difficulty in relaxing
  - Stiffness often pain often overlap
- Caused by lesions anywhere in neuraxis
  - CNS stiffness usually not painful
  - Can be difficult to localize

The Patient with Myalgia
Case 2
62 y.o. F with 20 yrs.
Muscle aching
STIFFNESS
No weakness
Several w/u negative
Worked at auto plant
? Overuse syndrome
Narcotics for pain
No weakness on exam
CK, EMG normal

Case 2 EMG

Muscle Stiffness
Differential Diagnosis
- Myotonic disorders
  - DM 1 & DM2
  - MC and PMC
  - Myotonia fluctuans
- Hypothyroidism
- Hypo PP
- Brody’s disease
- PMR
- Fibromyalgia

Myalgia Types
Aching
- By far the most common type of myalgia
- Dull, burning, deep aching
  - Can be difficult to localize in muscle
- Seen at rest, with exercise, after exercise
- May be localized (focal) or generalized
  - Diffuse pain more common for neurologists
  - Focal pains often screened out by others
**Deep Aching - Localized**

*Muscle Differential Diagnosis*

- Post-exercise myalgia ("weekend warrior")
- Infiltrating processes (e.g. tumor, sarcoid)
- Focal pressure necrosis
- Trauma
- Localized infections (bacterial, parasitic)
- Venous occlusion
- Arterial ischemia (thrombotic or embolic)
- Referred “muscle” pain

**Examples of Focal Myalgia**

[Sarcoid Myopathy][Diabetic Thigh Infarct]

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**Diffuse Myalgia**

*Inflammatory Muscle Disease*[^1]

[^1]: *Myth: Most PM/DM pts. have sig. myalgias (~25% do)*

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**Deep Aching - Generalized**

*Differential Diagnosis*

**With weakness**

- PM, DM (20-25%)
- Hypothyroidism
- Mitochondrial dx.
- Myotonic dystrophy 2
- Infectious myopathies
- Other rare myopathies

**Without weakness**

- Infectious myalgia (esp. viral)
- Toxic myopathies (eg lovastatin)
- MAD Deficiency
- PMR
- Fibromyalgia

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**Evaluation of Muscle Pain**

<table>
<thead>
<tr>
<th>Screening examination</th>
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<td>Labs. CBC, ESR, TFTs, lytes</td>
</tr>
</tbody>
</table>

| Neuro. eval - strength, endurance testing |
| Serum CK, electrodiagnostic studies |

| Normal |
| CK elevated |
| Weak, abn EMG, CK |

| Tender points present? |
| Tender points absent? |
| <5x nl |
| >5x normal, other sx |
| FET, Genetic testing |

| FM |
| PMR, MAD, Statins |
| Repeat |
| Biopsy |

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**The Patient with Myalgia**

*Case 3*

70 yo female, aches and pains since 2000

10 month history severe myalgias

AM stiffness, impairment of ADLs

Weakness getting out of chairs, rolling over in bed; sitting up

"I don’t feel good!"

10 pound weight loss; fatigue and lethargy

"I feel like I’m walking in glue"

Evaluations by 4 physicians negative

Referred for muscle biopsy; r/o PM
Case 3 – Supine to Sit

The Patient with Myalgia
Case 3
- Examination NORMAL, including strength
- Screening blood work normal
  - Including CK, aldolase
- EMG - completely normal (but painful)
- Muscle biopsy – type 2 atrophy
- ESR = > 100 mm/hour; diagnosis of PMR
- Prednisone 40 mgs/day
  - Complete resolution in 3-4 days

Polymyalgia Rheumatica

Epidemiology
- Technically not muscle disease per se
  - Periarticular inflammatory process
- One of most common causes of myalgia
  - Incidence of ~52.5/100,000 per year
  - 600-1000/100,000 in patients > age 50
- Mean age of onset 70 (90% > age 60)
- Female predominance of 3:1
- 50% of giant cell arteritis (GCA) get PMR
  - 10-20% of PMR develop GCA

Symptoms
- Dx. criteria “ongoing process”
- Myalgia, stiffness, aching
  - Neck, shoulders, hips
- Worse in AM, movement
  - Stiffness, “gelling”
- Systemic sx. in 40%
  - Fevers, depression, wt. loss, poor sleep, anemia, anorexia, arthritis
  - Similar to FM
- Tenderness rare (ddx FM.)

Laboratory
- CK and EMGs normal
- ESR, CRP both very high (mean ~90 for both)
  - 15-20% - normal ESR
- Temporal artery bx. only in patients with GCA sx
  - (not in isolated PMR)
- Muscle bx. not indicated
  - Non-specific changes
- Pathogenesis
  - Synovial pain

Chaang and colleagues
Diagnosis of polymyalgia rheumatica requires presence of all the following:
- Age 50 years or older
- Bilateral aching and stiffness persisting for 1 month or more affecting two of the following areas: neck or thorax, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs
- ESR > 40 mm/h
- Exclusion of other diagnoses except for giant cell arteritis

Healey
Diagnosis of polymyalgia rheumatica requires age greater than 50 years and presence of any three of the following:
- Pain in the neck, shoulder, or pelvic girdle
- Noticeable morning stiffness lasting more than 1 h
- Raised ESR
- Rigid response to low-dose prednisone or prednisolone (20 mg or less)

Presence of rheumatoid factor or antinuclear antibody excludes diagnosis of polymyalgia rheumatica

Kermani & Warrington. Lancet. 2013

Polymyalgia Rheumatica

Laboratory
Polymyalgia Rheumatica

**Treatment**

- Prednisone (10-40 mg/day) causes immediate and dramatic improvement in 12-48 hours
  - Diagnostic as well as therapeutic
- GCA requires higher doses
  - 60-100 mg orally or 1.0 gm IV
- Treat symptoms and ESR, CRP
  - Taper slowly when sx. under control
  - Usually requires 1-2 years treatment
- 10% require treatment for over 10 years!
  - Methotrexate drug of 2nd choice

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The Patient with Myalgia

**Case 4**

- 67 y.o. male former cocaine addict with 10 mo. hx. myalgia, weakness, acheing at times of bloody stools
  - Sx. progressed X 1 mo., CK ~1,500
- Muscle biopsy “mixed neurogenic/myopathic” changes
  - 6 mo. later, pain and mild weakness
  - 4+ - 5+ shoulder abductors, hip flexors
- Put on statins 6 mos before presentation!

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Statin Myopathy

**Terminology & Epidemiology**

ACC & AHA & NHLBI list 4 entities (2002)

- Statin myopathy – ANY muscle complaint
  - Up to 15-25% (including isolated CK rise ?)
- Statin myalgia – pain without CK rise
  - 2-9% overall (up to 20% in some series)
- Statin myositis – pain/weakness/CK rise
  - Rare with biopsy proven inflammation, < 0.2% cases
- Statin rhabdomyolysis – CK > 10x normal
  - < 1 per million scripts for all but cerivastatin (Baycol)

Since 105 million patients should be on statins
- 5-6 million new statin myopathy cases!! ? Underestimate!

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**Statin Myopathy Myths**

Franc et al, 2003

<table>
<thead>
<tr>
<th>Time to onset of muscle pain</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 days</td>
<td>4.5%</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td>24.8%</td>
</tr>
<tr>
<td>1-3 months</td>
<td>9.8%</td>
</tr>
<tr>
<td>3-12 months</td>
<td>12%</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>24.8%</td>
</tr>
</tbody>
</table>

- Symptoms can occur at any time in course!
- Symptoms do NOT always resolve with drug DC

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Statin Myopathy

**Predisposing Factors**

**Patient Factors**

- Increased age
- Female sex
- Small stature
- Liver, kidney dysfunction
- Hypothyroidism
- Post-operative
- Diet (eg grapefruit juice)
- Genetic predisposition
- Underlying myopathy

**Medication Factors**

- High statin dose
- Agent (eg lovastatin)
- Polypharmacy
  - Colchicine
  - Erythromycin
  - Cyclosporine
  - Niacin
  - Calcium channel blockers
  - Nefaxodone
  - Anti-fungals
  - Fibric acids (gemfibrozil)

Cause still unknown!

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Statin Myopathy

**Management**

- Tricky, since the meds ARE helpful
  - Cannot just blindly stop in all patients
- Rechallenge with other drug may be option
  - Usually doesn’t work!
- Symptomatic treatment (gabapentin, PT, NSAIDs, short course steroids)
- No evidence for exercise, CoQ10, carnitine
- “Tincture of time” (Zhao, AAN 2012)
  - Some patients have persistent symptoms!
Statin Myopathy

**Laboratory**
- CK may or may not be elevated & may not correlate with pain
- EMG may be myopathic
- Muscle biopsies often not helpful, even with high CK and abn EMG
  - Normal or non-specific myopathic changes
  - No inflammation
- May show necrotizing myopathy pattern

**Grable-Esposito et al Muscle & Nerve 2010**

- 25 pts. on chronic statins (only 4 with pain)
  - Weakness, high CK after statins DCd
  - Necrotizing myopathy on muscle bx.
- Responded to immunosuppressive drugs
  - 24 required multiple agents
  - 15 relapsed on withdrawal of agents

**Statin Myopathy**

**Necrotizing Myopathy**

- Mammen et al, Arth Rheum 2011 – autoantibodies to 100-kd antigen 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMGCR) protein. 45 patients; all with NM biopsy picture
  - 30/45 (67%) had taken statins; 1/3 had not!
- Mammen et al, 2012; anti-HMGCR Abs NOT found in the majority of statin-exposed, including those with self-limited statin myopathy.
  - May correlate with clinical manifestations
- Identifies subset of pts. with NM - ? clinical use?

**Statin Myopathy Management**

**Symptoms** (myalgia, CK, weakness)

- Sx. Resolve
- DC Statin
- Manage with diet, niacin, bile resins
- Treat symptoms
- Weakness
- Higher CK
- Progression
- Stable
- Persist
- Muscle bx.

**The Patient with Myalgia**

**Case 5**

38 yo WF - 3 yr. hx. muscle aches & pain
- Dull, aching soreness in most muscles
- Worse after almost any activity
- Complains of severe fatigue during ADLs
- PMH of depression, migraine HAs
- Referred for muscle biopsy
  - Presumptive diagnosis of polymyositis
- Fulfilled everyone’s criteria for fibromyalgia!

**Fibromyalgia – The Madness**

**Epidemiology**

- >6500 Medline articles since 1990!
- ≈2% population in US
  - (3.4% F; 0.5% M)
  - 3-6 mil. people in U.S.
- 75-90% cases in women
- Any age (children); especially elderly (7% of women > age 60)
- 20% of rheum. patients;
  - 3rd most common (after OA, RA)
Fibromyalgia

Notable Quotes

- “I don’t know what that term means.”
- “It’s just a waste-basket term.”
- “That’s just a grab-bag diagnosis.”
- “Doctor’s diagnose that when they really don’t know what’s wrong with someone.”
- “I don’t think it’s a ‘real’ disease at all.”
- “All these people are just depressed.”
- “They’re all trying to get disability.”
- “The horror…the horror”! (Dr. Kurtz)

Clinical Features

- Diffuse myalgia, stiffness, aching, joint pain
- Proximal predominance; can be anywhere
- Insidious onset (? post-infectious, trauma)
- Fatigue, morning stiffness, non-restorative sleep in 75% (similar to PMR)
  - Anxiety
  - Swelling
  - Headaches
  - IBS
  - Imbalance
  - Dysuria
  - Raynaud’s
  - Dysmenorrhea
  - Dysesthesias

ACR FM Classification Criteria

Wolfe et al, Arth Rheum, 1990

- Pain for 3 months
  - Both sides
  - Limbs & trunk
  - No other cause
- Tender points
  - 11 of 18 areas
  - 4 kg palpation (blanches nails)
  - Painful

Diagnostic Criteria Criticisms

- Need some experience in examination
- May be too inclusive
- May be too restrictive - patients with FM may not fulfill all criteria (eg 9/18 TPs)
- No “gold standard” for making diagnosis
- Problem of circular reasoning
- Similarities to headache criteria
- Like migraine HAs, just assigning name to a symptom complex

New ACR Diagnostic Criteria

Arth Care Res 2010;62:600-10

- Widespread pain > 3 mos.; no other cause
- Widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 OR
  - WPI of 3-6 and SS score ≥ 9
- NO tender point exam! 88% correlation

FM - Pathogenic Hypotheses

Summary

- FM is NOT a muscle dx. (50 neg. studies)
- FM is NOT entirely psych (30-50% with dx.)
- FM is NOT a single disease (multiple studies)
- May be “central sensitization syndrome” (dec. subs. P in CSF; dop. receptor polymorphism)
  - Sorensen (1995) - improved with IV ketamine (NMDA ant.) in blinded, cont. trial of 31 pts.
  - No imp. with IV lidocaine or morphine
- May be variation of small fiber neuropathy
25 FM pts. & nl controls
  ➢ 10 depression controls
  ➢ Tested with NPSI, QST, PREP, skin bx IENFD
  ➢ P < .01-.001 for all group comparisons
  ➢ 90% abnormal in 2/3 tests; 40% in all 3
  ➢ “.pointing towards neuropathic nature of pain in fibromyalgia”.

**Fibromyalgia Treatment**

<table>
<thead>
<tr>
<th>Beneficial</th>
<th>Possibly Beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Exercise</td>
<td>NSAIDs (used alone)</td>
</tr>
<tr>
<td>BCT</td>
<td>Zolpidem</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>Cyclobenzaprine</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Alprazolam</td>
</tr>
</tbody>
</table>

**Fibromyalgia Tentative Conclusions**

1. FM is clearly NOT a primary muscle dx.
2. FM is a “real” syndrome, as valid as any other in which criteria are clinical only.
3. FM is valuable concept for patient care
   ➢ Avoids unnecessary testing
   ➢ Provides frame of reference for patient
   ➢ Helps design therapeutic program
   ➢ Everybody knows what you’re dealing with
4. Diagnosis not diagnosis of exclusion

**Muscle Pain Summary**

- Consider carefully the type of pain
- Concentrate exam on strength testing!
  ➢ Evaluate further with CK, EMG, ESR
- Do NOT automatically biopsy
  ➢ Unrewarding most of the time!
  ➢ Only in selected cases
- Consider statin myopathy, MADD, PMR, FM in patients with “normal everything”.

**The Patient with Myalgia Bonus Case 6**

26 y.o. previously healthy exec. secretary
- Developed dull aching muscle pain
  ➢ Mainly on exertion
  ➢ First noted while training for a 10K race
- No other major complaints
- No myoglobinuria
- Examination, CK, EMG all normal
Forearm Exercise Test

**Method**

- IV in dominant antecubital vein (23 ga)
  - Kept open with heparin/saline boluses
- Draw baseline lactate and NH$_3$(on ice!)
  - Process quickly (<10-15 mintues)
- Squeeze ball MAXIMALLY for 1 minute
  - Cuff deflated
- Lactate, NH$_3$ at 1, 2, 4, 6, & 10 min
- Do NOT do ischemically (contracture)!

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FET – Case 6

[Graph showing lactate and NH$_3$ levels over time for Case 1, 2, and 3.]

- Flat lactate curve = glycolytic defect
- Flat ammonia curve = MADD

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Myoadenylate Deiminase Deficiency

**Histochemistry**

- Most common myo-enzyme deficiency
  - 2-3% of all biopsies; any age
- Myalgias, exercise intolerance
- CK normal or sl. high, EMG normal
- Flat NH$_3$, normal lactate rise on FET
- Biopsy: <2% MAD by biochemistry, IH
- Point mutations - AMPD gene (1p13-21)

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Myoadenylate Deiminase

**Biochemistry**

- Muscle-specific adenosine monophosphate deaminase (AMPD) – purine cycle
- Converts AMP to IMP by removing NH$_3$
  - IMP promotes ATP production
  - NH$_3$ helps buffer lactic acid
  - MADD: high AMP + low IMP + low NH$_3$ = pain
- 70-90% MADD have myalgia, exercise intolerance, fatigue. Myoglobinuria rare.
- MADD increased in pts. biopsied for myalgia

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Myoadenylate Deiminase

**But…**

- MADD pts have normal exercise capacity
- AMPD gene mutation in ~14% normals
- 1-2% of normal biopsies have MADD
  - Most are asymptomatic (MVP of muscle)
  - Association may be coincidental
- Point may be moot, since it is untreatable
  - Pt. satisfaction knowing they have “real” dx.; avoids FM label; lets you stop looking!
Evaluation of Muscle Pain

Screening examination
Labs. CBC, ESR, TFTs, lytes)

Neuro. eval - strength, endurance testing
Serum CK, electrodiagnostic studies

Normal
CK elevated
Weak, abn EMG, CK

Tender points present?
FM
PMR, MAD
Statins
Repeat
Biopsy

Tender points absent?
<5x nl
No other abn

>5x normal, other sx
FET, Genetic testing

Biopsy

Serum CK, electrodiagnostic studies

Strength, endurance testing