High Impact Rheumatology

Diffuse Arthralgias and Myalgias

Mary Beth Humphrey, MD, PhD
Professor of Medicine
Division Chief of Rheumatology
University of Oklahoma Health Sciences Center
OU Medicine Inc.
Disclosures

- I have no disclosures.
Objectives

1. Characterize inflammatory pain symptoms.
2. Differentiate autoimmune disease causes of muscle and joint pain from chronic pain syndromes.
3. Recognize common drugs associated with muscle pain.
Case 1: History

- A 48-year-old woman presents with diffuse muscle pain, weakness, and significant fatigue. She reports
  - Symptoms for over 3 years that have become slightly worse in past 6 months
  - Generalized pain and fatigue that limit her ability to work
  - Increasing sleep difficulty due to the pain
Case 1: Objective Findings

- General physical examination is unremarkable
- Diffuse muscle tenderness is noted
- Some tenderness around the joints, but no synovitis
- No objective muscle weakness
- Normal neurologic examination
- CBC, ESR, and chemistry profile are normal
How Should You Approach This Patient With Diffuse Musculoskeletal Complaints?

• Ask yourself the following questions:
  • Is this a systemic inflammatory rheumatic syndrome?
  • Does this represent rheumatic symptoms of an endocrinopathy?
  • Is this a toxic/drug reaction?
  • Is this a generalized soft-tissue pain syndrome?

NOTE: Do not overlook regional rheumatic pain syndromes (physical examination is critical)
Characteristics of Inflammatory Disease

• History
  • Associated with significant morning stiffness (>45 min)
  • Pain often better with movement
  • Insidious onset of the pain

• Physical exam
  • Objective findings of inflammation
    • Swelling, erythema, warmth, detectable joint fluid
  • Muscle weakness
  • Focal neurologic abnormalities
Characteristics of Inflammatory Disease (cont’d)

- Laboratory studies
  - ESR and C-reactive protein are indicators of generalized inflammation
  - Autoantibodies can be helpful in selected cases
  - Organ specific tests can suggest internal organ involvement
    - Liver function tests
    - Renal function tests
    - Muscle-specific enzymes
Inflammatory Causes of Musculoskeletal Pain: Specific Diagnoses

- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polymyositis
- Scleroderma/eosinophilic fasciitis
- Polymyalgia rheumatica

Duration of symptoms is important for diagnosis
- <6 months = may be early rheumatic disease
- 1 year = diagnostic clinical signs and lab abnormalities usually present
- >2 years = abnormalities almost always present
Musculoskeletal Pain in Older Patients

- Think polymyalgia rheumatica when
  - Age >60
  - Proximal muscle (shoulders and hips) myalgias and stiffness without specific muscle weakness
  - High ESR
  - Anemia
Think About the Musculoskeletal Pain of Endocrine Diseases

- Must consider
  - Thyroid disease
  - Parathyroid disease
  - Adrenal disease
  - Diabetes mellitus
  - Acromegaly
  - Vitamin D deficiency
- Diagnosis suggested by history and appropriate screening lab studies
  - TSH, calcium, phosphorous, glucose, sodium/potassium
Don’t Forget

- Patients with hypothyroidism can present with diffuse and nonspecific arthralgias and myalgias. CKs may be elevated.
Think About Toxic Drug Reactions That Can Cause Musculoskeletal Pain

- Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor
- Zidovudine (AZT)
- Ethanol
- Clofibrate
- Cyclosporin A
- Penicillamine
- Bisphosphonates
Don’t Forget

- Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors can cause severe myalgias with or without evidence of objective myositis
- More common now that everyone is on high dose statins

Think About Generalized Soft-Tissue Pain Syndromes

- Fibromyalgia syndrome primary or secondary to another illness
- Major depression associated with musculoskeletal pain
- Somatoform pain disorders
Soft-Tissue Pain Syndromes: Fibromyalgia

- Widespread musculoskeletal pain
- Decreased pain threshold and tolerance
- May have tenderness in specific regions (tender points)
- Associated fatigue, sleep, somatic complaints
- No objective inflammation seen on physical examination
- Normal laboratory findings
Pain Response in Fibromyalgia

MUSCLE GROUP

<table>
<thead>
<tr>
<th></th>
<th>Deltoid</th>
<th>Forearm</th>
<th>Calf</th>
<th>Thigh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>14</td>
<td>12</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

Relative Pain

- Deltoid: 14
- Forearm: 12
- Calf: 8
- Thigh: 10
Syndromes That Overlap With Fibromyalgia

The neurologist sees chronic headache, the gastroenterologist sees IBS, the otolaryngologist sees TMJ syndrome, the cardiologist sees costochondritis, the rheumatologist sees fibromyalgia, and the gynecologist sees PMS.
Significant depression is seen in:
- 49% of patients with chronic soft-tissue pain
- 37% of patients with rheumatoid arthritis
- 33% of patients with osteoarthritis

Depression is associated with increased pain levels in arthritis.

Depression is more prevalent with loss of valued activities.
Soft-Tissue Pain Syndromes: Somatoform Pain Disorders

- Chronic pain that cannot be explained by a known general medical condition
- These nonintentional symptoms cause significant distress and impairment of social, occupational, and functional activities
- Psychological factors play a role in the onset, severity, or maintenance of the pain
- Somatoform disorders are commonly seen (15%) and nonrecognized (71%) in the primary-care setting
- Outpatient screening diagnostic tools are available (PRIME-MD)

A patient probably has a generalized soft-tissue pain syndrome when there is

- Primarily nonarticular pain
- Marked fatigue and/or functional impairment
- No objective signs of inflammation or a general medical disorder on examination or laboratory studies
- Lack of specific neurologic abnormalities

- Specific diagnostic testing and therapy exist for many psychological causes of chronic pain
Case 1: Follow-up

- The laboratory studies were all normal
- The patient’s symptoms were present for 3 years
- Signs of focal, inflammatory, or organic disease were not found on physical exam
- PRIME-MD screening did not reveal evidence of significant depression or somatization
- Thus, the diagnosis of fibromyalgia was made
  - Remember: Systemic rheumatic syndromes have objective abnormalities
Case 2: History

- A 48-year-old woman presents with complaints of diffuse muscle pain, weakness, and fatigue. She reports:
  - Gradual onset over past 6 months
  - Morning stiffness lasting 2 to 3 hours
  - Difficulty with getting up out of a chair and combing her hair
  - No problems with holding a brush or standing on her toes
Case 2: Objective Findings

- Minimal muscle tenderness
- No joint tenderness or swelling
- Significant proximal muscle weakness in both upper and lower extremities
- No focal neurologic abnormalities
Case 2: Question

Based on these findings, which of the following diagnoses should be initially considered?

- A. Fibromyalgia
- B. Polymyalgia rheumatica
- C. Inflammatory myositis
- D. Noninflammatory myopathy
Case 2: Answer

- C and D. Inflammatory myositis or noninflammatory myopathy
  - The recent onset of symptoms (6 months) makes consideration of an inflammatory process likely
  - Proximal muscle weakness suggests a myopathy
  - PMR is characterized by muscle pain and stiffness, not objective weakness
Common Causes of Proximal Muscle Weakness With Elevated CK

- Inflammatory myositis
- Noninflammatory myopathies
  - Hypothyroidism
  - Hypokalemia
  - Alcoholism
- Drugs
  - AZT
  - HMG-CoA reductase inhibitors (the “statins”)

Polymyositis/Dermatomyositis: Key Points

- Proximal muscle weakness
- May have characteristic skin involvement
  - Heliotrope eyelids
  - Gottron’s sign
Polymyositis/Dermatomyositis

- Diagnosis confirmed by
  - CK levels
  - EMG findings
  - Muscle biopsy
  - Myositis antibodies
Polymyositis/Dermatomyositis (cont’d)

- Therapy
  - Prednisone 1–2 mg/kg, as initial therapy
  - Methotrexate or azathioprine is often added
  - Intravenous immunoglobulin in rapidly progressive or refractory cases

Don’t Forget

Symptoms of muscle weakness require a careful muscle strength and neurological examination.
Don't Hesitate to Refer

- The diagnosis of inflammatory muscle disease is difficult
- Prednisone therapy can cause a steroid myopathy with weakness
- Cytotoxic therapy is hazardous
- Failure to respond to therapy may suggest
  - Inclusion body myositis
  - Neoplasm-related myopathy
Case 3: History

- A 68-year-old man presents with complaints of diffuse muscle pain, weakness, and total body fatigue. He reports:
  - Gradual onset over past 6 months
  - Morning stiffness lasting 2 to 3 hours
  - Difficulty with getting out of a chair and combing his hair
  - Recent onset of right-sided headache
  - Recent onset of jaw pain when eating
Case 3: Objective Findings

- Proximal muscle tenderness without objective weakness
- Tender right temporal scalp region
- Normal visual acuity
- Hgb 9.8; ESR 85; CK 32
**Case 3: Question**

- Based on the clinical findings, what is the most important next step?

  A. Treat now with prednisone 5 mg bid, and observe

  B. Schedule a temporal artery biopsy for tomorrow morning and use the results to determine whether prednisone will be used

  C. Start an NSAID at maximal dose

  D. Treat now with prednisone at 40 to 60 mg per day and schedule temporal artery biopsy in the next few weeks
Case 3: Answer

- D. Treat now with prednisone at 40 to 60 mg per day and schedule temporal artery biopsy for next few weeks

- Patients with symptoms of PMR may have temporal arteritis
- Sudden visual loss may occur in TA
- The visual loss is usually not reversible
- Even with 6 weeks of treatment may still have positive biopsy

Temporal Arteritis and Polymyalgia Rheumatica

- Patients with PMR should be evaluated for symptoms of TA
  - Headache
  - Scalp tenderness
  - Visual changes
  - Jaw claudication
  - Visual hallucination (20%)
Treatment for GCA

- Treatment approaches for GCA
  - Prednisone 40 to 60 mg qd tapered slowly over 26-52 weeks
  - Tocilizumab (anti-IL6): 162mg subcutaneously once a week or every other week with rapid prednisone taper over 26 weeks

- Treatment approaches for PMR:
  - Prednisone 10 to 15 mg qd
  - NSAIDS at anti-inflammatory dosing (i.e. naproxen 500mg BID)
Tocilizumab treatment of GCA

![Graph showing patients without flare of Giant-Cell Arteritis (%) over weeks]

- **Tocilizumab weekly (N=100)**
- **Tocilizumab every other week (N=49)**
- **Placebo + 26-wk taper (N=50)**
- **Placebo + 52-wk taper (N=51)**

**No. at Risk**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
<th>48</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tocilizumab weekly</td>
<td>100</td>
<td>93</td>
<td>88</td>
<td>85</td>
<td>85</td>
<td>81</td>
<td>77</td>
<td>74</td>
<td>71</td>
<td>69</td>
<td>67</td>
<td>64</td>
<td>63</td>
<td>5</td>
</tr>
<tr>
<td>Tocilizumab every other week</td>
<td>49</td>
<td>47</td>
<td>45</td>
<td>40</td>
<td>40</td>
<td>39</td>
<td>35</td>
<td>32</td>
<td>30</td>
<td>30</td>
<td>29</td>
<td>26</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>Placebo + 26-wk taper</td>
<td>50</td>
<td>44</td>
<td>40</td>
<td>36</td>
<td>34</td>
<td>29</td>
<td>23</td>
<td>19</td>
<td>18</td>
<td>16</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Placebo + 52-wk taper</td>
<td>51</td>
<td>48</td>
<td>44</td>
<td>41</td>
<td>38</td>
<td>35</td>
<td>32</td>
<td>30</td>
<td>28</td>
<td>25</td>
<td>22</td>
<td>17</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

For probable temporal arteritis:

- **TREAT NOW! BIOPSY LATER!**

- Biopsy as soon as possible but can still be positive or show scarring up to 6 weeks of steroid treatment.
Case 4: History

- A 48-year-old woman presents with complaints of diffuse muscle pain, weakness, and fatigue. She reports:
  - Gradual onset over past 12 months
  - Recent separation from her husband
  - Difficulty sleeping
  - A 10-lb weight loss
- The physical exam and screening laboratory tests are normal
Case 4: Question

Based on this clinical information, which of the following diagnostic studies are now indicated?

- A. Abdominal CT to look for tumors
- B. ACTH stimulation test
- C. CPK, ANA, rheumatoid factor
- D. PRIME-MD Patient Questionnaire
Case 4: Answer

D. PRIME-MD Patient Questionnaire

- A simple outpatient tool for the screening of mental disorders in the primary care setting
- Presence of core symptoms of depression on this questionnaire correlates with DSM-IV diagnostic criteria
  - 97% sensitive
  - 94% specific

Screening for Depression in a Busy Clinic

• Screening question
  • “During the past month, have you often been bothered by the following?”
    • Little interest or pleasure in doing things (anhedonia)
    • Feeling down, depressed, or hopeless (depressed mood)
  • If one answer is “yes,” probe for core symptoms of depression

Screening for Depression in a Busy Clinic (cont’d)

- Core symptoms of depression = SALSA
  - “Have you experienced any of the following feelings nearly every day for the past 2 weeks?”
    - Sleep disturbance
    - Anhedonia
    - Low self-esteem
    - Appetite decrease
  - The presence of 2 or more core symptoms correlates with a diagnosis for major depression
Common Presenting Complaints With Major Depression

- Excessive worry over physical health
- Complaints of pain
  - Joint pain
  - Headaches
  - Abdominal pain
- Tearfulness and irritability
- Brooding and anxiety

Musculoskeletal pain and the presence of major depression may be interrelated.
Case 5: Question

- 40-year-old woman with diagnosis of fibromyalgia has quit her job because of pain and fatigue. Which of the following therapies is most important?

  - A. NSAIDs
  - B. Low-dose tricyclic agents at night (amitriptyline, cyclobenzaprine)
  - C. Instruction in general physical conditioning exercises
  - D. Encourage her to return to work
Case 5: Answer

C. Conditioning exercises

- NSAIDs a little better than placebo
- Amitriptyline a little better than NSAIDs
- NSAIDs plus amitriptyline a little better than amitriptyline alone
- Duration of response to pharmacological agents is usually limited
- But exercise is **BEST** of all - to increase function in spite of pain not to eliminate pain.
Therapy of Fibromyalgia Syndrome

- **Goal of therapy**
  - Keep patient functional in spite of pain

- **Therapeutic techniques**
  - Listen to the patient and reassure
  - Educate regarding the nondestructive nature of the disease
  - Aggressively treat coexisting depression
  - Emphasize appropriate sleep hygiene
  - Instruct in a regular conditioning exercise program
  - Encourage social interactions and employment
Use of corticosteroids or narcotic agents is ineffective and not indicated in fibromyalgia.
Things to Remember Tomorrow

- In patients with diffuse arthralgias and myalgias
  - Think about an inflammatory rheumatic syndrome
  - Think about an endocrine abnormality
  - Think about drug or toxic reactions
  - Think about a soft-tissue pain syndrome
    - Fibromyalgia
    - Depression
    - Somatoform pain disorder
Things to Remember Tomorrow

- Systemic rheumatic inflammatory syndromes have objective abnormalities on examination.
- Symptoms of muscle pain and/or weakness require a careful examination of muscle strength and focal neurological abnormalities.
- Screen for common, treatable mental disorders (PRIME-MD).