Spondyloarthridites

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Allan Morton’s
How to be a PCP or Internist

- If it’s working, don’t change it
- If it’s not working, change it
- If you don’t know what you’re doing, do nothing—most important
- And don’t call in a surgeon

Questions when seeing a patient with pain/arthritis/CTD

- Acute or chronic?
- Local or diffuse?
- Inflammatory or non-inflammatory?—morning stiffness/swelling
- Organic or functional?

PRESENTATIONS

- Pain with or without swelling
- Raynauds
- Constitutional symptoms, weakness, fatigue, etc.
- Rash—psoriasis, (+) photosensitivity, vasculitic, etc.
- Serositis
- Dysphagia/proximal or distal
- Dry eyes and/or mouth
- Abnormal lab—low WBC, platelets, proteinuria, polyclonal gammopathy, serology (ANA, RF, etc)

Program Outline

- Inflammatory Back Pain
- What are the Spondyloarthridites?
- Nomenclature
- Clinical Spectrum of the SpAs
- A Closer Look at Ankylosing Spondylitis
- Treatments
- Conclusions

Spectrum of the Spondyloarthridities

Low Back Pain

- Almost 50% of the population experience back pain in a year
- 80% of the population experience acute back pain at some time in their lifetime*

When is it inflammatory?


Inflammatory Back Pain

Patients with chronic back pain >3 months:
- Age at onset <40 years
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night with improvement upon arising

*www.asas-group.org (Assessment of Spondyloarthritis International Society)

What are the Spondyloarthridities?

- A family of inflammatory arthritidies that can involve:
  - Spine
  - Sacroiliac Joints
  - Oligoarticular peripheral arthritis
- HLA-B27+ genetic association
- Sites of inflammation:
  - Synovium
  - Entheses

Nomenclature

Definition 1: Enthesopathy

![Normal tendon attachment to bone](Normal tendon attachment to bone)

![Inflamed tendon attachment to bone](Inflamed tendon attachment to bone)


Anatomy of the Enthesis

- Specialized tissue composed of fibrocartilage
- Interface between tendon and bone
- Enthesis is a target of auto-immunity in HLA-B27 associated disorders
**Definition 2: Dactyliitis**

- Combination of:
  - Enthesitis
  - Tenosynovitis
  - Synovitis of the entire digit
- Asymmetric Distribution
- Associated with greater joint damage than non-affected digits


**Definition 3: Sacroiliitis**

- Inflammation of SI joints
- Can be associated with
  - Joint space erosions
  - Marrow edema
  - Sclerosis
  - Fusion
- Unilateral or Bilateral
- Often presents with low back pain or buttock pain
- Can mimic radicular pain

**Early Sacroiliitis**

**Advanced Sacroiliitis**

**Other Definitions: Inflammatory Eye Disease**

- Anterior Uveitis: Inflammation of anterior chamber
- Posterior Uveitis: Inflammation of posterior chamber
- Panuveitis: Inflammation in anterior & posterior chambers
- Iritis: Inflammation of the iris, a form of “anterior uveitis”
- Indocyclitis: Inflammation of iris and ciliary body
- Scleritis: Inflammation of sclera
- Synechiae: Adhesions of iris

**Clinical Features of the Spondyloarthridites**
Clinical Features of Spondylarthritides

- Sacroiliitis or spondylitis may be the dominant clinical feature
- Rheumatoid Factor Negative
- Peripheral arthritis often asymmetric
- Enthesopathy
- Extra-skeletal features include:
  - Eye: Uveitis
  - GI: Inflammatory Bowel Disease
  - Skin: Psoriasis

SpA and HLA-B27

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA-B27 Prevalence</th>
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<tbody>
<tr>
<td>Ankylosing Spondylitis</td>
<td>90</td>
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<tr>
<td>Reactive Arthritis</td>
<td>40-80</td>
</tr>
<tr>
<td>Juvenile Spondyloarthropathy</td>
<td>70</td>
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<tr>
<td>Enteropathic Spondyloarthropathy</td>
<td>35-75</td>
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<tr>
<td>Psoriatic Arthritis</td>
<td>40-50</td>
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<tr>
<td>Undifferentiated Spondyloarthropathy</td>
<td>70</td>
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<tr>
<td>Acute Anterior Uveitis</td>
<td>50</td>
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<tr>
<td>Aortic incompetence with heart block</td>
<td>80</td>
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</table>

Spondyloarthritis: Typical Manifestations

<table>
<thead>
<tr>
<th>Associated Manifestations</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory Back Pain</td>
<td>71-75%</td>
<td>75-80%</td>
<td></td>
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<tr>
<td>Enthesitis of Heel</td>
<td>16-37%</td>
<td>89-94%</td>
<td></td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>40-62%</td>
<td>90-98%</td>
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<tr>
<td>Dactylitis</td>
<td>12-24%</td>
<td>95-98%</td>
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<tr>
<td>Anterior Uveitis</td>
<td>10-22%</td>
<td>97-99%</td>
<td></td>
</tr>
<tr>
<td>Family Hx of SpA</td>
<td>7-36%</td>
<td>93-99%</td>
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<tr>
<td>Psoriasis</td>
<td>10-20%</td>
<td>95-97%</td>
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<tr>
<td>IBD</td>
<td>5-8%</td>
<td>97-99%</td>
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<tr>
<td>Good Response to NSAIDs</td>
<td>61-77%</td>
<td>80-85%</td>
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<tr>
<td>Elevated Acute Phase</td>
<td>38-69%</td>
<td>67-80%</td>
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<tr>
<td>HLA-B27 (axial involvement)</td>
<td>83-96%</td>
<td>90-99%</td>
<td></td>
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<tr>
<td>MRI (STIR)</td>
<td>90%</td>
<td>90%</td>
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</table>

Updated Concept of the Spondyloarthritides

- Predominantly Axial Disease
  - Ankylosing Spondylitis (radiographic SpA)
  - Non-Radiographic Axial SpA

- Predominantly Peripheral Disease
  - Reactive Arthritis
  - Psoriatic Arthritis
  - Inflammatory Bowel Undifferentiated SpA

Ankylosing Spondylitis

- Chronic, progressive immune-mediated inflammatory disorder
- Spine and SI-Joints are commonly affected sites
- Chronic inflammation leads to ankylosis of vertebral column and SI joints
- HLA-B27 + ~90%
- Enthesial involvement common

**Epidemiology of AS**
- AS 2-3 times more common in men
- Onset typically between ages 20 - 30 years
- Onset after age 40 is rare
- Prevalence in the population varies with region
- Best estimates: 1-9 per 1,000

**Psoriatic Arthritis**

**Psoriatic Arthritis**
- Skin disease most commonly pre-dates joint disease by 10 years
- Up to 30% of psoriasis pts will develop arthritis
- 20% of patients, joint disease is first symptom
- Estimated prevalence 3 per 1,000
- Equal male/female ratio
- RF negative
- Spine involvement seen in 40% of patients
- Spine involvement the sole manifestation in 5%

**Clinical Features of Psoriatic Arthritis**
- Psoriasis
- Dactylitis
- Enthesitis
- DIP Joint Involvement
- Sacroiliitis
- Spondylitis
- Nail Dystrophy

**BIOLOGICS FOR PsA**
- Remicade (Infliximab)—anti TNF
- Simponi Aria (Golimumab)—anti TNF
- Enbrel (Etanercept)—anti TNF
- Humira (Adalimumab)—anti TNF
- Cosentyx (Secukinumab)—anti IL17A
- Taltz (Ixekizumab)—anti IL17A
- Cimzia (Certolizumab)—anti TNF
- Stelara (Ustekinumab)—anti IL12/23
NON BIOLOGICS FOR PsA

- Otezla (Apremilast) — anti PDE 4
- Xeljanz (Tofacitinib) JAK inhibitor

Reactive Arthritis

- Sterile joint inflammation that develops 3-14 days after an infection
- Most commonly seen in young adults
- A systemic illness
- Strong association with HLA-B27
- Severity ranges from mild to disabling
- Spontaneous recovery is common

Clinical Manifestations of Reactive Arthritis

- Arthritis
- Gut Inflammation
- Eye Inflammation
- Carditis
- Urethritis Blanitis
- Nephritis
- Osteitis, Hyperostosis
- Enthesopathy
- Keratoderma blenorrhagicum
- Conjunctivitis
- Dactylitis
- Circinate Balanitis
- Enthesopathy
- Reactive Arthritis

Bacterial agents include: Salmonella, Shigella, Campylobacter, Yersinia, Chlamydia, Neisseria, Borrelia and Strep
**Enteropathic Arthritis**

- Arthritis occurs in 10-22% of patients with inflammatory bowel disease
- Arthritis may precede GI presentation by several years
- Bowel inflammation may perpetuate joint inflammation
- Peripheral arthritis more common in patients with colonic involvement


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**Peripheral Arthritis**

- Pauci-articular, asymmetric
- Can be migratory
- Activity often correlates with activity of IBD
- Often with non-erosive attacks lasting days to weeks
- Often resolves with colectomy

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**Axial Arthritis:**

- Sacroiliitis
- Inflammatory Spondylitis
- Axial disease not influence by GI activity

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**Undifferentiated SpA**

- Signs and Symptoms of inflammatory back disorder
- Pt does not meet criteria for AS or other spondyloarthropathy
- Some have mild intermittent symptoms
- Many patients over time evolve to develop:
  - AS
  - Inflammatory Bowel Disease
  - Psoriasis or Psoriatic Arthritis

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**Ankylosing Spondylitis**

A Closer Look
Onset of RA vs AS

German rheumatological database: disease duration ≤5 years; 1993 to 1998 data. Used with permission.

Delay in Diagnosis of AS

Average delay in diagnosis: 8.8 years
Delay in HLA B27 + was 8.5 years
Delay in HLA B27 – was 11.4 years

Delay in diagnosis leads to worse clinical outcomes and increases disability

Enthesitis: A Hallmark Lesion in AS

- Inflammation of the enthesis typical feature of AS
- Common sites of enthesial inflammation:
  - Achilles tendon
  - Plantar fascia
  - Pelvis
  - Tibial tubercles
  - Costochondral junctions
  - Elbow epicondyles
- Relevance of enthesitis to synovitis, subchondral marrow inflammation, and osteitis unclear
- Enthesal fibrocartilage major target of immune response and primary sites of immunopathology

Impact of smoking on early axial SpA

- 708 pts with IBP < 2 y (mean 1.5)
  - 647 met ≥1 criteria for AS
  - 37% smokers
- Smoking was associated with worse disease:
  - MRI findings in smokers
    - MRI findings in smokers
  - SI inflammation 1.57 < 0.001
  - Spinal inflammation 2.33 < 0.001
  - SI structural change 1.54 0.002
  - Spinal structural change 2.02 0.01

Suggests smoking may be both a prognostic factor and pathogenic factor

Enthesitis

Achilles Tendon Right Heel

AS: Signs and Symptoms

Peripheral Manifestations

Enthesis
Peripheral arthritis
Dactylitis

50% patients with enthesitis
Up to 58% patients ever had arthritis
Much smaller number of patients

2Sidiropoulos PI et al. Rheumatology 2008;47:680-681
Dactylitis

Dactylitis and Enthesitis
Why are they important?

Enthesitis often first manifestation of peripheral disease
Dactylitis associated with erosive disease

Ankylosing Spondylitis: A Debilitating Rheumatic Disease
Over time, joints in the spine can fuse together and cause a fixed, bent-forward posture

Ankylosing Spondylitis
"Bamboo Spine"
Repeated process of healing and bone formation leads to formation of syndesmophytes 'bone bridges'

AS: Extra-articular Disease

- Acute Anterior Uveitis
  - Common affects 25-30%
  - Acute attacks typically unilateral
  - Eye pain, redness, impaired vision, photophobia

- Cardiovascular
  - Aortic regurgitation
  - Ascending aortitis
  - Conduction abnormalities
  - Pericarditis
  - Cardiomegaly
  - Increased cardiovascular risk

- Pulmonary
  - Apical Fibrosis
  - Restrictive Lung Disease
  - Insidious, progressive

- G.I.
  - Enteric Mucosal Lesions
    - Typically subclinical
    - Seen in 60% of AS
  - Ulcerative colitis or Crohn’s will develop 10-15% of time

- Renal
  - IgA Nephropathy
  - Secondary Amyloid

AS: Extra Articular Disease
Ankylosing Spondylitis: Iridocyclitis with Synechiae

Common Constitutional Symptoms of AS
- Anorexia
- Malaise
- Low Grade Fever
- Weight Loss
- Fatigue

Fatigue is a frequent complaint of patients with AS²

AS: Quality of life
- Bad QoL¹
  - Pain
  - Sleep problems
  - Fatigue
  - Loss of mobility & dependency
  - Loss of social life
- Effect employability¹
- Higher rate of mortality²

Treatment

Goals of Treatment for SpA
- Controlling Signs & Symptoms
  - Pain
  - Morning stiffness
  - Fatigue
  - Extra-articular disease
- Preserving Function
  - Spinal mobility
  - Activities of daily living
- Minimizing Structural Damage
  - Osteoporiferation and ankylosis
  - Osteoedresorption
- Minimizing Socioeconomic Impact
  - Sick leave
  - Disability

Treatment Options for SpAs
- NSAIDs—peripheral arthritis, axial disease, enthesitis, dactylitis
- DMARDs—peripheral arthritis, skin
- Biologics (anti-TNF, anti IL17A)—peripheral arthritis, axial disease, enthesitis, dactylitis, skin
- Physical therapy—axial disease, enthesitis

¹ Adapted from Ward M. Arthritis Care & Res 1999;12:247-254
² Adapted from Ann Intern Med 2007;146:305-8, 359-361; Linden UD et al. Chapter 10 In: Firestein, Budd, Harris, McInnes, Ruddy and Sergent, eds. Kelley’s Textbook of Rheumatology: Spondyloarthropathies. 8th ed. Saunders Elsevier;2009:p.1178

Stiffness Pain Fatigue Poor Sleep

<table>
<thead>
<tr>
<th>Percentage of Patients (%)</th>
<th>N=175</th>
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<tbody>
<tr>
<td>Stiffness</td>
<td>30.2</td>
</tr>
<tr>
<td>Pain</td>
<td>83.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62.4</td>
</tr>
<tr>
<td>Poor Sleep</td>
<td>54.1</td>
</tr>
</tbody>
</table>

AS mean duration: 23.7 yr

High socioeconomic consequences

10
NSAIDs for AS

- High efficacy reducing clinical symptoms
- NSAIDs are disease modifying in AS:
  - Retardation of spinal radiographic progression
  - Retardation only seen in subjects with elevated CRP or Sed Rate and syndesmophytes at baseline
  - Continuous use more effective than "on-demand" use


TNF blockers inhibit progression of atherosclerosis in AS

- AS associated with increased cardiovascular risk
- 67 pts had measurement of Intima-Media Thickness (IMT) of carotid arteries at BL and 5 yr
- IMT did not change in 56 pts who remained on TNFi compared to 11 pts who stopped therapy
- Conclusion: TNFi might stabilize or slow IMT progression, reflecting decreased cardiovascular risk

Van Sijl et al. ArthRheum.2012; 64 (Suppl) abstract 1702

Clinical Pearls

- Prolonged morning back stiffness may be suggestive of an inflammatory back problem
- Consider the SpAs when seeing patients with a chronic enthesitis such as plantar fasciitis, Achilles tendonitis, costochondritis or tennis elbow
- These disorders often appear between the ages of 20-40

Conclusions

- The Spondyloarthritides are a group of inflammatory arthropathies that are common.
- The SpAs are frequently overlooked or misdiagnosed
- These disorders are associated with significant morbidities and an increase in mortality
- New therapies have dramatically changed the approach to these disorders

UPDATE IN RHEUMATOLOGY

- Cases
- Rheumatoid Arthritis
- Fibromyalgia
- NSAIDs
- Questions

Case #1

- 42 y/o female presents with joint pain
- Morning stiffness about 60 minutes
- Difficulty making a full fist in the morning
- Swelling of both wrists and several MCPs and PIPs
- History compatible with Raynauds
- PE—synovitis of wrists, several PIPs, and MCP tenderness
Diagnosis? An inflammatory polyarthritis

What lab tests do you want to order?

- CBC, platelet count
- Chemistry profile
- UA
- ESR or CRP
- ANA with titer and pattern
- Rheumatoid factor
- Anti CCP

Results

- All normal except ESR at 37.
- So what does she have? An inflammatory polyarthritis. Why not SLE? Because ANA is positive >95% of the time in Lupus
- Does a negative RF and anti CCP rule out RA—NO
- What if her RF is positive? Most likely RA

Anti-CCP (Cyclic Citrullinated Peptide) Antibody: Specificity and Sensitivity

- Positive CCP antibody: almost always means RA
- If not: almost certainly a closely related auto immune connective tissue disease

Laboratory Findings in RA

- Rheumatoid Factor
  - Early on: May be negative
  - Eventually positive in 80% of patients
  - Positive rheumatoid factor: 8% of the general population
- Anti-cyclic citrullinated peptide antibody (CCP)
- ANA: present in approximately 40% of RA patients
- Erythrocyte sedimentation rate
- C-reactive protein
- Anemia of chronic disease, thrombocytosis, leukocytosis

Case #1a

- 42 y/o female presents with joint pain
- Morning stiffness about 60 minutes
- Difficulty making a full fist in the morning
- Swelling of both wrists and several MCPs and PIPs
- History compatible with Raynauds
- PE—synovitis of wrists, several PIPs,
Let’s say all the lab is the same except she has a positive ANA 1:640 with a speckled pattern

What lab tests next?

- Anti double stranded DNA
- Anti Sm
- Anti RNP
- Anti Scl 70
- SSA, SSB if dry eyes and/or dry mouth

Results
- Anti DNA negative
- Anti Sm negative
- Anti RNP positive
- Anti Scl 70 negative

Diagnosis??

Mixed Connective Tissue Disease
- SLE
- Polymyositis
- Scleroderma

Case #2
- 37 year old male with low back pain for 7 years. Back pain radiates down either leg to the knee but not below. Low back morning stiffness 2 hours
- History of heel pain
- History of iritis
- Lab??

Routine as in case #1—CBC, Chemistry, Platelet count, UA, ESR or CRP,
- HLA B27 antigen
- Would you order other lab like ANA, RF, anti CCP?
**Spondylarthritides**

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Enteropathic arthritis
  - Crohn’s disease
  - Ulcerative colitis
- Juvenile ankylosing spondylitis

**HLA-B27 disease associations**

- Ank spondylitis  >  90% (white males)
  - with uveitis or aortitis ~100%
- Reactive arthritis  50-80%
  - with sacroiliitis or uveitis  90%
- Juvenile spondylarthropathy  80%
- Inflammatory bowel disease
  - Peripheral  Not increased
  - Axial
    - Crohn’s disease  50%
    - Ulcerative colitis  70%
- Psoriasis
  - Peripheral  Not increased
  - Axial  50%

**Case #3**

- 73 year old female comes to the ER with acute onset pain and swelling of her right knee for the past 36 hours
- No history of trauma
- Denies fever and chills
- History of chronic pain in both hands (DIPs, PIPs, and 1st CMCs), low back, and neck
- Active synovitis and warmth of the knee

**WORK-UP**

- X-ray of the knee
- Lab—CBC, Uric acid, chemistry profile, ESR or CRP, synovial fluid analysis
- If you suspect a systemic inflammatory arthritis or CTD with a monoarticular presentation you might order ANA, RF, and anti-CCP

**Synovial fluid results**

- Fluid is cloudy, can’t read newspaper print through it
- Low viscosity—negative string sign
- WBC 27,000; mostly polys
- Calcium pyrophosphate dihydrate crystals
CLASSIFICATION OF SYNOVIAL FLUID—WHAT TO ORDER—3 Cs

- Cell count with diff
- Culture
- Crystal analysis

RHEUMATOID ARTHRITIS

Characteristics of RA

- Affects young people
  - Peak age of onset: 20-45 years
  - Not rare in seniors
- Affects approximately 1% of the population
- Affects 3 million Americans
- 2-3 times more common in women
- Loss of physical function and quality of life
- Life expectancy reduced
- Don’t forget seniors

Be Mindful of Warning Signs

- Morning stiffness ≥1/2 hour
- Joint pain lasting ≥3 months
- Symmetrical painful and/or swollen joints
- ≥3 swollen joints
- Hand, wrist, foot involvement
- Positive squeeze test
- RF+
- CCP +

Laboratory Findings

- Rheumatoid Factor
- Anti-CCP—more specific than RF
- ANA: present in about 40% of RA patients
- Acute Phase Reactants—correlates only 40-60 percent of the time
  - Sed Rate
  - CRP
- CBC:
  - Anemia of chronic Disease
  - Thrombocytosis
  - Leukocytosis

Anti-CCP

- High specificity for RA
- Often associated with more aggressive disease
- When seen in combination with a + RF, diagnosis of RA virtually certain
RA associated with increased morbidity and mortality

- 2 times more likely to have an M.I.
- 70% more likely to have a stroke
- 70% more likely to develop an infection
- 4 times more likely to develop NH lymphoma
- Mortality rates 41% higher in women
- Life expectancy shortened on average by 7 yrs


Comorbidities with RA

- Infection
- Malignancies
- Cardiovascular Disease

Early Referral Algorithm for Newly Diagnosed RA

Rapid evaluation advised with clinical suspicion of RA, which may be supported by the presence of any of the following:

- ≥3 swollen joints
- MTP/MCP involvement
  - Positive squeeze test
- Morning stiffness ≥30 minutes


The Treatment of Rheumatoid Arthritis

Medications Used to Treat RA

- NSAIDs
- DMARDs
  - Methotrexate (Rheumatrex)
  - Hydroxychloroquine (Plaquenil)
  - Lefluonamide (Arava)
  - Sulfasalazine (Azulfidine)
- Biologic Disease Modifiers
- Corticosteroids

Conclusion

- Rheumatoid Arthritis is a serious disease
- Early diagnosis is the key to good outcomes
- Advent of new therapies have major impact in altering disease progression
FIBROMYALGIA

A Disease of Exclusion

- Disease overview
- Pathophysiology
- Clinical features
- Treatment

Does it exist??
How is it diagnosed??
Can it be treated successfully??
I like to distinguish between primary and secondary fibromyalgia: primary—no cause; secondary—associated with another disease

Proposed Etiology of Fibromyalgia

- Genetic component of FM
  - Specific gene mutations may predispose individuals to FM
  - Polymorphisms in the COMT enzyme and the serotonin transporter
- Environmental factors that may trigger the onset
  - Physical trauma or injury
  - Infections
  - Psychological stressors
- FM may occur concurrently with arthritis (OA), autoimmune diseases (RA, SLE), and hypothyroidism

Pathophysiology of Fibromyalgia: Overview

- Central pain mechanisms
  - CNS mechanisms (i.e., central sensitization)
  - Increased levels of excitatory neurotransmitters (glutamate and substance P) may contribute to neuronal hyperactivity and central sensitization
  - Compared with normal controls, CSF levels of substance P are 3-fold higher

Despite extensive research, the pathogenesis of pain in FM is not clearly understood. However, central sensitization has emerged as a leading theory of disease mechanisms.
Clinical Features of Fibromyalgia

**WIDESPREAD PAIN**
- Chronic, widespread pain is the defining feature of FM
- Patient descriptors of pain include aching, exhausting, nagging, and burning

**SLEEP DISTURBANCES**
- Characterized by nonrestorative sleep and increased awakenings
- Abnormalities in the continuity of sleep and sleep architecture
- Reduced slow wave sleep
- Abnormal alpha wave intrusion in non-REM sleep

**TENDERNESS**
- Presence of tender points
- Most patients also have tenderness to pressure, heat, cold, electric pain

**FATIGUE/STIFFNESS**
- Morning stiffness and fatigue are common characteristics of FM

Fibromyalgia Is Often Associated With Sleep Disturbances

- Nonrestorative sleep is common
- Insomnia, early morning awakenings, and poor-quality sleep
- Alpha intrusion is a common but nonspecific EEG finding in FM patients
  - May interfere with sleep function and contribute to worsening of pain after sleep
  - Can induce FM with sleep deprivation

**CONDITIONS I CONSIDER**
- Connective tissue diseases
- Inflammatory arthritides
- Occult malignancy
- Hormonal disease—thyroid, diabetes, etc.
- Polymyalgia rheumatica
- Depression/functional disease

**Diagnostic testing**
- Lab—CBC, chemistry profile, ESR or CRP, UA, ANA, RF, TSH, Vitamin D level
- X-rays and scans—chest, bone scan?, abdominal US or CT scan

- LOOKING FOR OCCULT DISEASE!!

**PEARL**
- Patients often need a diagnosis. If you are comfortable with the diagnosis of fibromyalgia in your patient, make the diagnosis, educate the patient, and initiate treatment

**DRUGS APPROVED FOR FM**
- Pregabalin (Lyrica)
- Duloxetine (Cymbalta)
- Milnacipran (Savella)
**BOTTOM LINE IN FM MANAGEMENT**

- Make the diagnosis
- Educate and reassure the patient—non crippling, non deforming pain in the ....
- Fibromyalgia Network Newsletter
- Fibromyalgia support groups??
- Assist with sleep

**DRUGS I USE TO TREAT FM**

- Flexeril
- Elavil
- Approved drugs like Lyrica and Cymbalta
- Mild analgesics
- Sedatives if necessary
- I try to avoid opioids

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**The NSAID Debate: Exploring the Risks and Benefits**

**NSAID Use and Selection**

*Important Considerations*

- Age
- Concomitant use of aspirin
- Risk for NSAID renal toxicity
  - Avoid in CKD, stages 4 and 5
  - Use with caution in patients with:
    - CKD stage 3
    - Risk for intravascular volume depletion with reduced renal perfusion (e.g., congestive heart failure, cirrhosis)
- Risk for NSAID GI toxicity
- Risk for NSAID CV complication


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**NSAID Use on the Rise in the United States**

- 2000: 50
- 2008: 133

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**Assessment for NSAID GI Toxicity Risk 2009 ACG Guidelines**

**High Risk**

- History of previously complicated ulcer, particularly recent history
- Multiple (>2) risk factors

**Moderate Risk (1-2 risk factors)**

- Age > 65 years
- High-dose NSAID therapy
- Prior history of uncomplicated ulcer
- Concurrent use of aspirin (including low-dose), anticoagulant, or corticosteroids

FDA Strengthens NSAID CV Warning

- Risk of heart attack or stroke can occur as early as the first weeks of using an NSAID
- The risk appears greater at higher doses and with longer duration of use
- Estimates of increased risk range from 10 percent to 50 percent or more, depending on the drugs and the doses studied
- NSAIDs can increase the risk of heart attack or stroke in patients with or without heart disease or risk factors for heart disease
- Patients with heart disease or risk factors have a greater likelihood of heart attack or stroke following NSAID use
- Increased risk of heart failure with NSAID use


Common Primary Care Scenarios

- GI and CV risks increase with age
- Who should receive a gastric cytoprotective agent?
  - Generally, at age 65 or older, but it is important to consider each patient individually
- Who requires careful consideration due to CV risk?
  - Patients older than 65 years of age
  - Naproxen is useful option
- Balance of risk/benefit assessment

PRECISION TRIAL

- Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen and Naproxen
- 10 year trial

PATIENTS WITH INCREASED CARDIOVASCULAR RISK

- Patients > 18 years old with OA or RA requiring NSAID
- Established CV disease or increased risk for CV disease
- Duration of follow-up: mean 34 months (mean treatment 20 months)
- Mean patient age 63 years, female 64%, Diabetics 35%
- Celecoxib 100 mg BID (n=8072) (up to 200 mg BID in RA patients)
- Ibuprofen 600 mg TID (n=8040) (up to 800 mg TID in RA patients)
- Naproxen 375 mg BID (n=7969) (up to 500 mg BID in RA patients)

PRIMARY OUTCOME INCIDENCE CV DEATH, MI, OF STROKE

SECONDARY OUTCOME: GI EVENTS OR RENAL EVENTS

- PRIMARY:
  - Cardiovascular events: 2.3% of celecoxib vs 2.7% of ibuprofen vs 2.5% of naproxen

- SECONDARY:
  - GI events: 1.1% for celecoxib, 1.6% for ibuprofen, 1.5% for naproxen
  - Renal events: 0.7% for celecoxib, 1.1% for ibuprofen, 0.9% for naproxen

INTERPRETATION

- Increased CV risk patients celecoxib was noninferior to ibuprofen or naproxen in regard to CV safety
- Fewer documented GI events with celecoxib compared with ibuprofen or naproxen, and fewer renal events compared with ibuprofen
- Limitation of the trial include 69% discontinuation and overall low event rate (77% did not have established CV disease)
- Dispelled notion that naproxen is the safest nonselective NSAID
WHAT YOU NEED TO KNOW ABOUT NSAIDs

- COX 2 NSAIDs are not associated with higher incidence of cardiovascular disease than traditional NSAIDs
- There are differences among medical associations regarding recommendations for use of NSAIDs
- All NSAIDs can be associated with hypertension
- Some traditional NSAIDs may block the anti-platelet effect of aspirin
- The use of aspirin with all NSAIDs can increase GI AEs
- All NSAIDs, including Celebrex, are associated with increased risk of serious GI AEs, but COXIBs have been shown to be less
- All NSAIDs are similar in efficacy