Ankylosing Spondylitis: Overarching Concerns
New Concepts and New Treatment for Spondyloarthritis

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What is Ankylosing Spondylitis

The word is from Greek ankylos meaning stiffening, spondylos meaning vertebra, and -itis meaning inflammation.

The cause of ankylosing spondylitis is unknown however, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism is believed to be autoimmune or autoinflammatory. Diagnosis is typically based on the symptoms with support from medical imaging and blood tests.

AS is a type of seronegative spondyloarthropathy meaning that tests show no presence of rheumatoid factor (RF) antibodies.

Famous people with Ankylosing Spondylitis

- Dan Reynolds lead singer with Imagine Dragons.
  - His story “started in my hips. I couldn’t move and felt drilling in my nerves”
  - Scariest moments when he “could not get out bed”
  - When he was first diagnosed he was newly married and then had a baby.
  - Misdiagnosed by “lots of Doctors”
  - Finally saw rheumatologist and “got on medicine and now I am in remission”
  - He is now 29 and came forward with his disease
  - “The disease has taught me a lot about life and ‘gave me compassion’, taught me discipline”.
  - It has given me “more passion for life”
  - Now is a spokesperson for AS and thisisaslife.com

What is Spondyloarthritis?

is an umbrella term for inflammatory diseases that involve both the joints and entheses—the sites where the ligaments and tendons attach to the bones.

The most common of these diseases is Ankylosing Spondylitis
And includes many others

Learning objectives

1. Discuss new concepts of the natural history of the AxSpA
2. Differentiate between old and new criteria for diagnosis of axial SpA
3. Explain the role of conventional radiography and MR imaging, lab testing and genetic markers
4. Adopt management strategies using older and newer pharmaceutical agents
Spondyloarthritis - More common than RA?

"Axial spondyloarthritis may be as prevalent as rheumatoid arthritis"

- 2009-2010 NHANES
  - 6,684 screened ages 20-69
  - 5,106 interviewed
  - 20% of Americans have low back pain
  - 6% have inflammatory low back pain
  - axSpA 0.9-1.4% prevalence

Rheumatoid prevalence 0.6%-1%
axSpA 0.9-1.4%
Could it be that we are underdiagnosing?

Come in to my office.
You’ll see a lot more of this
than this.
Why?

New concept of AS and Related Spondyloarthritis (SpA)

<table>
<thead>
<tr>
<th>Predominately Axial Disease</th>
<th>Predominately Peripheral Disease</th>
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<tbody>
<tr>
<td>Ankylosing spondylitis (radiograph SpA)</td>
<td>Reactive arthritis ReA</td>
</tr>
<tr>
<td>Nonradiographic Axial SpA (nr-AxSpA)</td>
<td>Psoriatic arthritis PsA</td>
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<td>Inflammatory bowel disease-associated arthritis</td>
<td>Undifferentiated SpA</td>
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Index of Background terms

- SpA
- axSpA
- nr-SpA (undifferentiated SpA)
- ASAS
- PsA
- ReA (Reiter’s)
- AS
- Spondyloarthritis
- Axial spondyloarthritis
- Non-radiographic axial spondyloarthritis
- Assessment of Spondyloarthritis International Society
- Psoriatic Arthritis
- Reactive Arthritis
- Ankylosing Spondylitis

There Are More Than 100 Forms of Arthritis
Epidemiology of Rheumatic Diseases

- 1 in 8 persons has osteoporosis
- 1 in 10 persons has osteoarthritis
- 1 in 33 persons has fibromyalgia
- 1 in 100 persons has RA
- 1 in 350 persons has PsA
- 1 in 100 persons has ankylosing spondylitis

+ IBD arthritis
+ Undiff. Sacroiliitis
+ ReA Reactive arthritis

- 1 in 2000 persons has systemic lupus erythematosus
- 1 in 10,000 persons has scleroderma
Case study

- 39 year old Caucasian male referred for LBP
- CC: Acute onset of Low back and bilateral buttock pain after skiing 5 weeks previously.
- HPI: In addition to low back and buttock pain he complains of neck soreness and then the discomfort went to his mid back between his shoulder blades and then his hips. It became difficult to breathe and had anterior chest pain.
- PMHx: History of Crohn’s disease, anemia, hypertension, CKD stage III with negative renal biopsy, except scarring likely due to hypertension.

Case Study

- Labs:
  - ESR-85 mm/hr
  - CRP-46.0 mg/L ULN 10
  - BMP-CREAT 1.89 mg/Dl
  - BUN-31 mg/Dl
  - HLA B-27 negative
  - RF-negative
  - ANA-negative
  - CBC-Hgb 11.7 Hct 31.2

Radiology

- X-ray bilateral hip and SIJ:
  - Impression: sclerosis and irregularity of bilateral SIJs consistent with sacroiliitis

Case History

Radiology

- X-ray thoracic spine: Impression
  - There is mild curvature of the thoracic spine with convexity to the left in the lower thoracic spine. This curvature was not present in 10/27/2008.

Epidemiology of AS

- AS is 2 to 3 times more common in males than in females
- Symptoms usually start between 20 and 30 years of age
- Most patients with AS are either diagnosed late or already compromised upon diagnosis
- The mean delay in the diagnosis of AS ranges between 5 to 11 years

Etiology of AS

- Precise etiology unclear
- Strong genetic predisposition highlighted by familial occurrence and HLA-B27
  - ~ 50% of the risk of developing AS is from HLA-B27
  - However HLA B-27 is not necessary or sufficient to cause the disease
- Twin studies show susceptibility of 90%
- Recurrence risk ratios of developing AS in a 1° relative is ~8%
1. Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest.
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes.
3. Limitation of chest expansion relative to normal values correlated for age and sex.

Radiological criteria:
Sacroiliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally.

Definite AS:
If the radiological criterion is associated with at least 1 clinical criterion.

van der Linden S., Arthritis Rheum. 1984;27:361-368

Modifed New York Criteria for AS 1984
Clinical criteria:
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ASAS classification for Axial spondyloarthritis
SpA
In patients with > 3mths of back pain and age at onset <45 yoa.

Sacroiliitis on imaging plus ≥ 1 SpA feature
HLA-B27 + plus ≥ 2 other SpA features
SpA features
• Inflammatory back pain
• Ankylosis
• Enthesitis (heel)
• Uveitis
• Dactylitis
• Psoriasis
• Crohn’s disease/colitis
• Flex of SpA
• Elevated CRP

Sensitivity 82.9%
Specificity 84.4%

Rudwaleit 2009

Approach to diagnosis of axial spondyloarthritis
Chronic low back pain (5% probability of axial SpA)
Yes (14% probability)
No (2% probability)

HLA-B27

Rheumatologist:
Evaluation of clinical SpA
(Enthesitis, uveitis, buttock pain, Peripheral arthritis, dactylitis, Psoriasis, Crohn’s, + NSAID response
-Acute phase reactants
-HLA-B27
-Imaging (x-ray MRI)

Judgement on probability of axial SpA
No further testing
Unless SpA strongly suspected

Clinical Conceptualization of the Natural History of axSpA: An Emerging Model

Diagnosis of AS
• Establishing the diagnosis is often difficult.
• The presenting manifestations can be wide ranging.
• Thus, a variety of health care professionals may see these patients.

- Primary care providers
- Ophthalmologists
- Podiatrists
- Other medical and surgical specialists (pain practices, orthopods)
- Rheumatologists
axSPA
Other features outside the spine

• Asymmetric oligoarthritis
• Psoriasis
• Uveitis
• Enthesitis

No radiographic evidence at early stages

Enthesitis
Hallmark of AS

• Enthesis=attachment of tendon, ligament or joint capsule. Enthesis is a complex structure that appears to be a principal site of inflammation of SpA

• Enthesitis can be an early and prominent feature of SpA

• Inflammation in AxSpA primarily affects the sacroiliac joints and axial skeleton

• Bony tenderness occurs from enthesitis at many other sites-costosternal, spinous process, greater trochanter, iliac crests, and ischial tuberosity, tibial tubercles or heels.¹²


Asymmetric oligoarthritis

Inflammatory Enthesitis

Direct and consensual photophobia to light in left eye
25-40% develop this sign

Sacroiliitis on Pelvis film Stage III

Irregular borders
Fluffy boney appearance
Narrowing
Sacroiliitis by MRI

Normal SI joint x-ray
Pt had sx of inflammatory back pain for 2 yr

Thick Arrows: Subchondral marrow inflammation shown by increased MRI signal

Thin Arrow: Joint cavity

Case study of pt. with 2 years of symptoms

What is the role of MRI in AS?
- Chronic low back for > 3 months
- Started before the age of 45
  - 5% chance of having SpA

So in this age of cost control and concern regarding ordering expensive tests what do you do?

Then H and P should include
- Does the patient have a family history or past history of AS/SpA?
- Does the patient have inflammatory back/buttock pain? - increases odds to 14%
- Does the patient have difficulty touching his/her toes?
- Are they tender over one or both SIs?
- Do they have a + Schober test?
  In this situation if either HLA-B27 is + or abnormal x-ray or MRI then Odds are increased or the Dx can be made

Pathology of AS
AS is characterized by 2 key pathological findings: inflammation at the enthesis and new bone formation in the sacroiliac joint and in the spine

AS sequence of events
- Enthesitis/Osteitis
- Bone resorption
- Bone remodeling
- New bone formation and ankylosis

Schematic sequence of events in AS vs RA

RA response vs Spondyloarthritis
1. Rheumatoid is catabolic
   - Cartilage loss
   - Erosions
2. Spondyloarthritis catabolic plus anabolic
   - Anabolic causes syndesmophyte formation
   - And ankylosis of joints

**Genetic Marker**

**HLA-B27**

- AS Caucasians 90% + for HLA-B27

**Mechanism of action**

Four major hypothesis¹

1. MHC class I antigen presentation in HLA-B27+ pts
   - Molecule misfolds
   - Result-more easily recognized by natural killer cells

2. HLA-B27 can modulate the human microbiome
   - cross reacts with certain gram negative bacteria
   - as seen with reactive arthritis
   - high prevalence of subclinical intestinal inflammation in AS patients

**Treatment options**

- Other Biologic Response Modifiers
  - Abatacept
  - Rituimab
  - Tocilizumab
  - Tofacitinib

All approved for RA but no significant results in AS.³

**Treatment options**

- Physical therapy
  - Extension exercises, weight maintenance/reduction

- Smoking cessation-restrictive disease due to chest wall involvement

- NSAIDs important role
  - Majority 50% or > response

- DMARDs limited role
  - Sulfasalazine-may be useful in peripheral arthritis
  - Methotrexate-no efficacy
  - Leflunomide-no efficacy

**Newer treatment options for AS**

- Secukinumab- IL-17A inhibitor
  - Indications: AS, PSO, PSA
  - Dosage-150 mgs Q 1 week for 4 as induction
  - Then 150 mgs monthly
  - Side effect profile- same as TNF inhibitors
  - TB screening
  - Avoid live vaccines
  - Pregnancy category B

**Newer treatment options for PSO**

- Ixekizumab- IL-17A inhibitor
  - Indications: PSO
  - Dosage-80 mgs 2 SQ week 0, then 80 mgs 2,4,6,8,10,12 then Q 4
  - 80 mgs monthly
  - Side effect profile- slight uptick in IBD associated symptoms in pts with IBD.
  - TB screening
  - Avoid live vaccines
  - Pregnancy no data
2010 ASAS/EULAR Recommendation for Management of AS

- Non-pharmacologic therapy
  - Patient education
  - Regular exercise
  - Physical therapy land or water based
  - Patient association and self help groups may be useful
- Extra-articular manifestations psoriasis, uveitis, IBD should be managed with collaboration of appropriate specialists

- Rheumatologists and PC should be aware of increased CV risk and Osteoporosis risk

Immunizations in SpA

- Live virus vaccines should be avoided in patients on immunomodulators:
  - Intranasal influenza, mumps/measles/rubella (MMR), yellow fever, typhoid, oral polio
  - Wait at least 2 weeks after giving these vaccines before initiating immunomodulators
- Zoster vaccine should be avoided in patients on biologic agents
  - May be given to patients on MTX and prednisone <20 mg/d
- Other immunizations are safe:
  - Influenza (injection), tetanus, pneumococcus, meningococcus, hepatitis A, hepatitis B, H. influenzae B (HiB), human papillomavirus (HPV)

How do you make the diagnosis of SpA?

- Several important key factors:
  - You must think of it in any pt. male or female who has chronic low back pain. Have the pt point to the pain and decide clinically where it is.
  - The history is key, labs and imaging are also helpful
    - Ask the questions-IBD, iritis, psoriasis, FMHx, inflammatory back pain
    - Get labs including HLA-B27
    - Order an SIJ film and if negative with a high suspicion then order MRI
    - Try NSAIDs and if no response then refer
    - Consider referral to rheum for dactylitis, migratory joint pain and psoriasis, inflammatory back pain, enthesitis, FMHx of SpA, iritis, or unexplained erosions seen on x-ray evaluation.
**Tasks ahead unanswered questions**

- With earlier detection can we alter the disease and damage it does?
- MRI scanning of SI joints can be vital in earlier diagnosis
- Are NSAIDs and TNF inhibition the best way to achieve remission as defined by preventing osteoproliferation and fat infiltration?

Personalize treatment is possible with improved understanding of the genetics and baseline characteristics that can predict response.

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**Thank You!**

Questions?

Questions?  
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