RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

RHAPP NATIONAL CONFERENCE

SEPTEMBER 8-10, 2022

The Crisis of Undiagnosed Axial Spondyloarthropathy

Robert Laugherty, JD, MBA, PA-C

Disclosure Policy

All individuals in control of the content of continuing education activities provided by the Annenberg Center for Health Sciences at Eisenhower (ACHS) are required to disclose to the audience all relevant financial relationships related to the content of the presentation or enduring material. Full disclosure of all relevant financial relationships will be made in writing to the audience prior to the activity. All other staff at the Annenberg Center for Health Sciences at Eisenhower and RhAPP have no relationships to disclose

Disclosures

- Contract Speaker: Eli Lilly and Amgen

September 2008

Yi E et al. *Rheumatol Ther*. 2020; 7: 65-87.

September 2017

Yi E et al. *Rheumatol Ther*. 2020; 7: 65-87.

Journey to a Diagnosis

- Confounding Comorbidities
  - Diabetes
  - Obesity
  - CVD
  - Infection (discitis, osteomyelitis)
  - Osteoporosis (compression Fx)
- Frequently Misdiagnosed
  - OA
  - Fibromyalgia
  - Depression/Anxiety

Journey to a Diagnosis

- Onset of chronic back pain at younger than 45 years old
- Inflammatory vs. Mechanical
- Associated Signs and Symptoms
  - Uveitis
  - Inflammatory bowel disease
  - Asymmetrical Arthritis
  - Elevated ESR or CRP
  - Positive response to NSAIDs

What Are r-axSpA and nr-axSpA?

Depends on When You Asked the Question!

Rome Criteria (1961)

- Lower back pain that lasts for 3 months or longer and improves with exercise but not with rest
- Limited lumbar mobility
- Limited chest expansion
- Pain and stiffness in the middle of the spine
- A history of uveitis
- Grade 2 sacroiliitis on both sides
- No corrections based on a person’s age or sex for spine and chest mobility

New York Criteria (1966)

- Clinical Criteria
  1. Limitation of motion of the lumbar spine in all three planes: anterior flexion, lateral flexion, and extension
  2. History or the presence of pain at the dorso-lumbar junction or in the lumbar spine
  3. Limitation of chest expansion to 1 in. (2.5 cm) or less, measured at the level of the fourth intercostal space

New York Criteria (1966) Cont.

- Radiologic criteria: SI joint x-rays were given numerical scores depending on the severity of the sacroiliitis
  - Grade 0: normal
  - Grade 1: some blurring of the joint margins – suspicious
  - Grade 2: minimal sclerosis with some erosion
  - Grade 3: definite sclerosis on both sides of the joints OR severe erosions with widening of joint space with or without ankylosis
  - Grade 4: complete ankylosis

New York Criteria (1966) Cont.

- To make the diagnosis must fulfill any of the following:
  - Grade 3 or 4 bilateral sacroiliitis with at least one clinical criterion
  - Grade 3 or 4 unilateral sacroiliitis with Clinical criteron #1 or with both Clinical Criteria #2 and #3
  - Grade 2 bilateral sacroliitis with Clinical criterion #1 or with both clinical criteria #2 & #3
  - To meet the "probable" AS diagnosis, a patient would have grade 3 to 4 bilateral sacroiliitis without any clinical criteria

Modified New York Criteria (1984)

- Clinical criteria:
  - Low back pain and stiffness for more than 3 months which improves with exercise but is not relieved by rest
  - Limitation of motion of the lumbar spine in both the sagittal and frontal planes
  - Limitation of chest expansion relative to normal values corrected for age and sex
- Radiologic criterion:
  - Sacroiliitis grade 2 bilaterally or sacroiliitis grade 3-4 unilaterally
- Definite AS diagnosis is met if the radiologic criterion is associated with at least one clinical criterion

The Assessment of Spondyloarthritis International Society (ASAS) 2009

ASAS Criteria (2009)

- **Back pain lasting >3months starting under the age of 45 and:**
  1. Radiological diagnosis of sacroiliitis plus one or more features of spondyloarthritis
  2. HLA B27+ plus two or more features of spondyloarthritis
- **Features:**
  - Inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis, ulcerative colitis/Crohn's, response to NSAIDs, Family Hx of SpA, Elevated CRP
- **Allows for classification of r-axSpA and nr-axSpA based on presence or absence of radiologic evidence**

Journey to a Diagnosis (Cont.)

AVERAGE TIME TO DIAGNOSIS

5-14 YEARS!

Prevalence

- 19% of adults in the US have chronic back pain
- 5% of patients with chronic back pain are estimated to have axSpA
- 16% of patients with inflammatory back pain are estimated to have axSpA
- 6% of US population is HLA B27 + (5.8% Male, 6.6% Female)
  - 7.5% White, 4.6% Hispanic, 1.1% African American

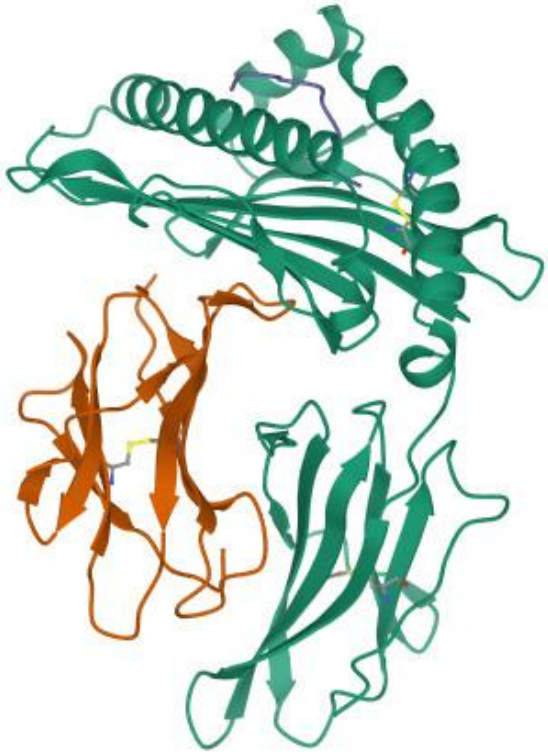
Prevalence (Cont.)

- AxSpA affects 1.7-2.7 million people in the US
- 40%-60% of patients diagnosed with axSpA have nr-axSpA
- Spectrum of nr-axSpA to r-axSpA
  - 60%-90% will remain in nr-axSpA
  - 10%-40% of nr-axSpa will progress to r-axSpA in 2-10 years
  - Of those who transition from nr-axSpA to r-axSpA, 60%-70% will have progressive disease

Case Study – Meet Cassidy

- 32-year-old white/Italian female recently married
- Lower back pain for 10 years, worsening over the last 18 months
- Sent by PCP for positive ANA (1:80h) and oral ulcer
- 2+ hours of morning stiffness and pain level 4-6/10
- Increasing fatigue
- Desire to start a family
- Also has long-term right shoulder pain and history of right lateral epicondylitis
- No known family history of autoimmune disease
- Has been using OTC Ibuprofen, chiropractic and massage with little relief

Pathophysiology




6'6"
6'0"
5'6"
5'0"
4'6"
4'0"
3'6"
3'0"
the
Usual Suspects

Pathophysiology

- The usual suspect cells
  - Dendritic Cells, Macrophages, Naïve T Cells, Th1 Cells, Neutrophils, iNKT Cells, γδT Cells, CD3+/CD4-/CD8- T cells
- The usual suspect cytokines
  - IL-17, IL-22: Enthesitis
  - IL-17, IL-23, TNF: Joint Inflammation
  - IL-17, TNF, RANKL: Bone Erosion
  - IL-17, IL-22 Osteoprolifiration


The
unusual
suspects

Pathophysiology (Cont.)

- The Mysterious Role of HLA B27
- 105 Subtypes (HLA B27:01 – HLA B27:106)
- The most common subtypes associated with axSpA
  - HLA-B*27:05 (Caucasians)
  - HLA-B*27:04 (Chinese)
  - HLA-B*27:02 (Mediterranean populations)

Pathophysiology (Cont.)

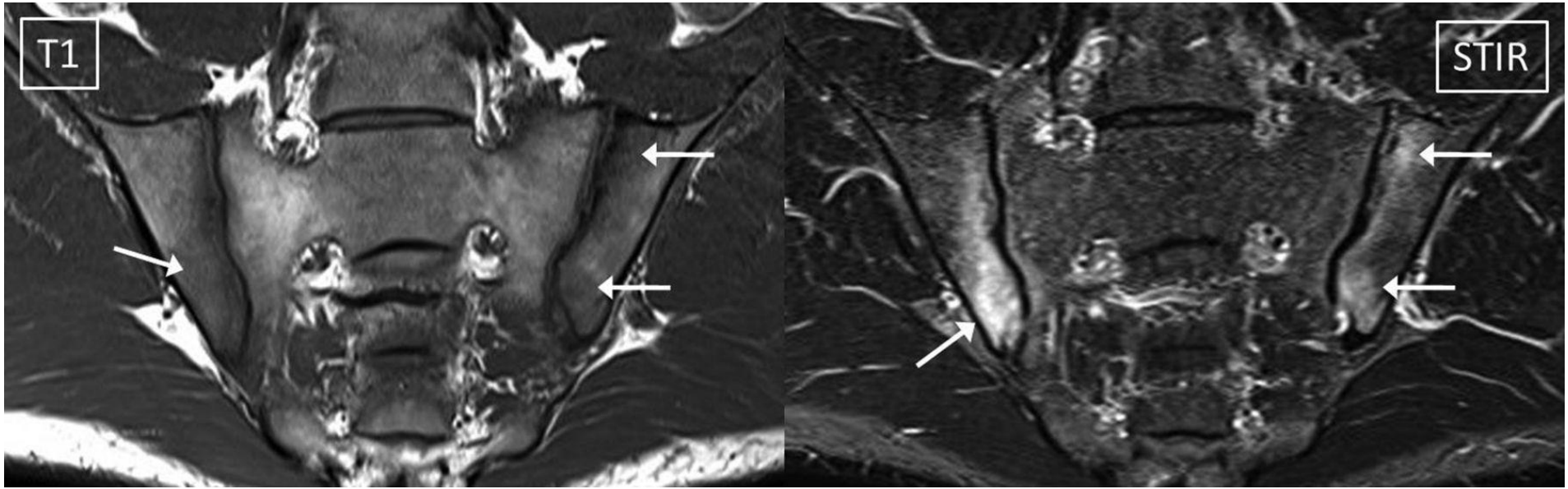
- **Hypotheses of why HLA B27 plays such an important role**
  - Bacterial dysbiosis: altered intestinal microbiome
  - β2microglobulin deposits triggering tissue destruction
  - Cell surface homodimers activate release of proinflammatory cytokines
  - UPR/Protein misfolding increases production of proinflammatory cytokines
  - CD8+T cells cross react creating arthritogenic peptides
  - Altered immune response with other members of MHC-1 members

Meet Cassidy (Cont.)

- **Pertinent Physical Exam/Lab Findings:**
  - HLA B27 positive, repeat ANA 1:80h – all sub-serology negative
  - No fever, rashes, alopecia or eye inflammation
  - Oral aphthae x2
  - Right shoulder ACJ crepitus and SAB tenderness, Yergason (-)
  - Chest Expansion: 9 cm (normal 5-13 cm)
  - Occiput to wall: 0 cm
  - Schober's Test: 8 cm (normal >5 cm)
  - Normal hip ROM but pain with external rotation
  - Bilateral Sacroiliac joint tenderness
  - 8/18 muscular tender points
  - No peripheral joint swelling or tenderness
  - 5/5 Muscle strength

Sacroiliac Joint Imaging

Sacroiliac Joint Imaging (Cont.)



Cassidy (Cont.)

- **Differential Diagnosis**
  - Non-radiographic axial SpA
    - No plain film structural changes
  - Psoriatic Arthritis
    - History of recurrent tendonitis
  - Behcet's
    - Mediterranian Ancestry and oral aphthae
  - Right shoulder RTC partial tear
  - Fibromyalgia

Currently Available Medications

- NSAIDs/COX-2 inhibitors
- Glucocorticoids
- SSZ
- MTX (only if predominantly peripheral disease)
- Anti TNF inhibitors: (infliximab, etanercept, adalimumab, Golimumab, certolizumab*)
- IL-17A Inhibitors: (ixekizumab*, secukinumab*)
- Janus Kinase Inhibitors: (tofacitinib, upadacitinib)

ACR-SPARTAN-SAA
Treatment Guidelines

Beyond Genetics

- Gut microbiome is different in AS and IBD-AS than in IBD or normal controls
- Can differentiate between AS and IBD just by using stool microbiome
- Compromised epithelial barrier integrity leads to decreased tight junction proteins in SpA patients ("leaky-gut")
- Explaining the incomplete predictive ability of HLA B27 by looking at epi-genetics and DNA methylation of Th17 cells

Cassidy (Cont.)

- Final Diagnosis: nr-axSpA
  - She also did have a right partial rotator cuff tear
- Treatment Considerations
  - Child-bearing capability, desires to have a child with-in the next 12-18 months
  - Will need to monitor for CTD due to positive ANA and Hx of oral aphthae
  - No Hx of using a cDMARD or bDMARD in the past
- Trial of SSZ was ineffective and caused some nausea
- Certolizumab was chosen due to proven safety in pregnancy
  - Clowse et al. Largest TNF-inhibitor pregnancy exposure cohort study

Diagnosis: **Why So Long?**

- Age of onset (average age at onset is 25 – 28 years old)
- Insidious Onset/Pain Pattern
- Diagnosis vs Classification
- Spinal Pain affects 80% of the US population at some point in life
- Chronic back pain affects 13% of US adult population
- Majority of AS patients are managed by non-rheumatology provider
- Only 37% of AS patient are Dx by Rheumatology
- Limitations of physical exam
- Lack of reliable biomarkers

Current Ongoing Clinical Trials for axSpA

- Terbinafine Treatment of Axial Spondyloarthropathy (allylamine antifungal)
- Evaluate the Preliminary Efficacy, Safety, and PK of Subcutaneous JS005 in Chinese Adult Patients With Active AS (IL-17A)
- A Study to Evaluate the Efficacy and Safety of SHR0302 in Patients With Ankylosing Spondylitis (JAK 1)
- Jaktinib Hydrochloride Tablets In The Treatment of Active Ankylosing Spondylitis (AS) (JAK 1,2,3)

Current Ongoing Clinical Trials for axSpA

- ABY-035 in the Treatment of Subjects With Ankylosing Spondylitis (IL-17)
- A Study of CC-99677 in Participants With Active Ankylosing Spondylitis (AS SpA axSpA) (p38-mitogen activated protein kinase inhibitor)
- Efficacy and Safety of SHR-1314 in Patients With Active Ankylosing Spondylitis (IL-17A)
- A Study to Evaluate the Efficacy and Safety of Bimekizumab in Subjects With Active Nonradiographic Axial Spondyloarthritis

...And Now for Something Completely Different

- Efficacy and Safety of Fengshi Gutong Capsule in patients with active ankylosing spondylitis: A 4-week randomized controlled, double-blinded, double-dummy trial
  - 37% ASAS 20 response in FSGTC and FSTGC+NSAID groups compared to 27.5% in NSAID only group
- TNF inhibitors have a protective role in the risk of dementia in patients with ankylosing spondylitis: Results from a nationwide study
  - AS is positively associated with Alzheimer's Disease, Parkinson's Disease and Epilepsy
  - AS patients treated with TNF inhibitors have lower rates of Alzheimer's Disease

References

- Danve, A., Deodhar, A. Axial spondyloarthritis in the USA: diagnostic challenges and missed opportunities. Clin Rheumatol 38, 625–634 (2019)
- Clowse MEB, Scheuerle AE, Chambers C, et al. Pregnancy Outcomes After Exposure to Certolizumab Pegol: Updated Results From a Pharmacovigilance Safety Database. Arthritis Rheumatol. 2018;70(9):1399-1407. doi:10.1002/art.40508
- https://www.centerwatch.com/clinical-trials/listings/condition/469/ankylosing-spondylitis
- https://clinicaltrials.gov/ct2/home
- Arthritis & Rheumatology Vol. 71, No. 10, October 2019, pp 1599–1613Deodhar A, Strand V, Kay J, et al
- Deodhar A, Strand V, Kay J, et al. The term ‘non-radiographic axial spondyloarthritis’ is much more important to classify than to diagnose patients with axial spondyloarthritis; Annals of the Rheumatic Diseases 2016;75:791-794
- Aggarwal et al. Distinctions between diagnostic and classification criteria? (2015) Arthritis Care & Research Vol. 67, No. 7, July 2015, pp 891–897
- Bennett, P. H., and Burch, T. A. (1968) Idem, pp. 305-313 – and Wood, P. H. N. (1968) Idem, p. 456

References (Cont.)

- Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777–83.
- van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-8.
- Zhu, W., He, X., Cheng, K. et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res 7, 22 (2019)
- https://www.medicalnewstoday.com/articles/ankylosing-spondylitis-diagnostic-criteria
- Watad A, McGonagle D, Anis S, et al. TNF inhibitors have a protective role in the risk of dementia in patients with ankylosing spondylitis: Results from a nationwide study. Pharmacol Res. 2022;182:106325. doi:10.1016/j.phrs.2022.106325
- Xie Y, Tu L, Zhang Y, et al. Efficacy and safety of Fengshi Gutong Capsule in patients with active ankylosing spondylitis: A 4-week randomized controlled, double-blinded, double-dummy trial. J Ethnopharmacol. 2022;285:114731. doi:10.1016/j.jep.2021.114731
- Kellgren, J.H., Jeffrey, M. R., and Ball, J. (eds) (1963) “The Epidemiology of Chronic Rheumatism”. Vol. 1, p. 326. Blackwell, Oxford

References (Cont.)

- Sternes, P.R., Brett, L., Phipps, J. et al. Distinctive gut microbiomes of ankylosing spondylitis and inflammatory bowel disease patients suggest differing roles in pathogenesis and correlate with disease activity. Arthritis Res Ther 24, 163 (2022)
- Beterams, A., Calatayud Arroyo, M., De Paepe, K. et al. In vitro triple coculture with gut microbiota from spondyloarthritis patients is characterized by inter-individual differences in inflammatory responses. Sci Rep 12, 10475 (2022)
- Xiao, M., Zheng, X., Li, X. et al. Integrative blood-derived epigenetic and transcriptomic analysis reveals the potential regulatory role of DNA methylation in ankylosing spondylitis. Arthritis Res Ther 24, 15 (2022)
- Rodriguez EM. Autoimmun Infect Dis. 2016;2(3)
- Reveille JD. Genetics of spondyloarthritis--beyond the MHC. Nat Rev Rheumatol. 2012;8(5):296-304. Published 2012 Apr 10. doi:10.1038/nrrheum.2012.41
- Chen, B., Li, J., He, C., Li, D., Tong, W., Zou, Y., & Xu, W. (2017). Role of HLA-B27 in the pathogenesis of ankylosing spondylitis (Review). Molecular Medicine Reports, 15, 1943-1951. https://doi.org/10.3892/mmr.2017.6248

References (Cont.)

- McGonagle DG, McInnes IB, Kirkham BW, et al. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: recent advances and controversies; Annals of the Rheumatic Diseases 2019;78:1167-1178
- Aggarwal, R., Ringold, S., Khanna, D., Neogi, T., Johnson, S. R., Miller, A., ... & Feldman, B. M. (2015). Distinctions between diagnostic and classification criteria?. Arthritis care & research, 67(7), 891
- Deodhar, A. (2014). Axial spondyloarthritis criteria and modified NY criteria: issues and controversies. Clinical rheumatology, 33(6), 741-747

Thank you