Juvenile Spondyloarthropathies

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Objectives

• Definition
• Classification of spondyloarthritis
• Epidemiology of juvenile spondyloarthritis and psoriatic arthritis
• Clinical manifestations and course
• Imaging and labs
• Treatment
The name...

- Spondyloarthropathy
- Spondyloarthritis
- Spondyloarthritides
- Seronegative enthesopathy and arthropathy syndrome
- Pelvispondylopathy
Definition

Group of pediatric rheumatic diseases characterized by enthesitis and arthritis involving in most cases, the lower extremities in the initial years, and, in a variable proportion of cases, the sacroiliac and spinal joints some years later.

Types of Spondyloarthritis

- Juvenile Spondyloarthritis
  - Ankylosing Spondylitis
  - Undifferentiated Arthritis
  - Psoriatic Arthritis
  - Reactive Arthritis
  - IBD arthritis

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Lumpers vs. Splitters
Lumpers vs. Splitters

I'm a splitter! Lumper!
Who has SpA?

- Depends on who you ask:
  - NY criteria for ankylosing spondylitis
  - Modified NY criteria for ankylosing spondylitis
  - European Spondyloarthropathy Study Group (ESSG) criteria
  - Modified ESSG criteria
  - Amor criteria
  - ILAR JIA enthesitis-related arthritis or psoriatic arthritis criteria
  - Garmisch–Partenkirchen criteria
  - SEA syndrome criteria
  - Atypical SpA in children criteria
  - Vancouver juvenile psoriatic arthritis criteria
Classification Warfare

Much of rheumatology remains mired in the 19th century when it comes to classifying autoimmune and inflammatory disorders….we revisit classification criteria every few years to determine whether they can be improved, but are these revisions necessary and useful?

Robert P. Sundel

Sundel RP. Nat Rev Rheumatol. 2012
Inflammatory back pain (ASAS 2009 definition)

- Age at onset <40 years
- Insidious onset
- Improvement with exercise
- No improvement with rest
- Pain at night (with improvement on rising)
Modified NY criteria for Ankylosing Spondylitis

Table 1 Modified New York criteria for ankylosing spondylitis ref. [3]

A. Diagnosis*

1. Clinical criteria
   a) Low back pain and stiffness for more than three months, which improves by exercise, but is not relieved by rest
   b) Limitation of motion of the lumbar spine in both the sagittal and frontal planes
   c) Limitation of chest expansion relative to normal values correlated for age and sex

2. Radiological criterion:
   Sacroiliitis grade ≥2 bilaterally or grade 3–4 unilaterally

B. Grading

1. Definite ankylosing spondylitis is considered if the radiologic criteria is associated with at least one clinical criterion
2. Probable ankylosing spondylitis if:
   a) Three clinical criteria are present
   b) The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered)

Radiographic criteria
Grade 0 = normal
Grade 1 = suspicious changes
Grade 2 = minimal abnormality – small localized areas with erosions or sclerosis, without alteration in the joint width
Grade 4 = severe abnormality – total ankylosis.

The proportion of children and adolescents that fulfill these criteria before they reach the age 17 years is probably <15%.

ASAS classification criteria for axial spondyloarthritis

Back pain of ≥3 months’ duration and age at onset <45 years

PLUS

Sacroiliitis on imaging and ≥1 feature of SpA

OR

HLA-B27 and ≥2 other features of SpA

*Sacroiliitis on imaging
- active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA
- definite radiographic sacroiliitis according to mod NY criteria

#SpA features
- inflammatory back pain
- arthritis
- enthesitis (heel)
- uveitis
- dactylitis
- psoriasis
- Crohn's/colitis
- good response to NSAIDs
- family history for SpA
- HLA-B27
- elevated CRP

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ASAS classification criteria for peripheral spondyloarthritis

In patients with ≥3 months back pain (with/without peripheral manifestations) and age at onset <45 years:

- Sacroiliitis on imaging plus ≥1 SpA feature
- HLA-B27 plus ≥2 other SpA features

In patients with peripheral manifestations ONLY:

- Arthritis* or enthesitis or dactylitis
  - ≥1 SpA feature
  - uveitis
  - psoriasis
  - Crohn’s/ulcerative colitis
  - preceding infection
  - HLA-B27
  - sacroiliitis on imaging
  - OR
  - ≥2 other SpA features
  - arthritis
  - enthesitis
  - dactylitis
  - IBP ever
  - family history for SpA

*Peripheral arthritis: usually predominantly lower limb and/or asymmetric arthritis
Combined sensitivity 79.5%, combined specificity: 83.3%; n=975

### ESSG classification criteria

**Table 5 European Spondylarthropathy Study Group classification criteria and results of their validation in children**

| Inflammatory back pain or synovitis – symmetric or predominantly in the lower limbs plus |
| one of the following |
| • Positive family history |
| • Psoriasis |
| • Inflammatory bowel disease |
| • Urethritis, cervicitis, or acute diarrhea within one month before arthritis |
| • Buttock pain alternating between right and left gluteal areas |
| • Enthesopathy |
| • Sacroiliitis |

Validated in 361 adults with SpA and 455 controls, such criteria showed a sensitivity of 86.7% and specificity of 87.0% ref. [38].

Validated in 2,982 rheumatic children ref. [74], the diagnostic properties of those criteria were 78.7% for sensitivity, 92.2% for specificity, 58.8% and 96.8% for positive and negative predictive values, respectively, 85.3% for positive likelihood ratio, and 90.3 for diagnostic accuracy. Sensitivity of the criterion “inflammatory back pain” was only 9.1% in children.
Enthesitis-related arthritis (ILAR)

- Arthritis and enthesitis

- Arthritis or enthesitis and at least 2 of the following:
  - Sacroiliac joint tenderness and/or inflammatory spinal pain
  - Family history of HLA-B27-associated disease in a 1st degree relative
  - Acute anterior uveitis
  - Onset of arthritis in a boy ≥6 years

- ERA exclusions: psoriasis in patient or 1st degree relative; IgM RF; systemic arthritis; arthritis fulfilling two JIA categories
Genetics of Spondyloarthritis

- 60-80% of children with spondyloarthritis have HLA B27.

- 5% of the HLA B27-positive population develop AS.

- 20% of HLA B27-positive relatives of patients with spondyloarthritis develop disease.

- Variations in other genes such as \( ERAP1 \) y \( IL23R \) are associated with AS.
A brief look into pathogenesis
Epidemiology of juvenile spondyloarthritis

- It's a different animal than adult AS.

- ERA+PsA = 10-20% of JIA

- 10-20% of adult patients with spondyloarthritis begin with symptoms before age 16.
JIA subtypes

- Systemic: 4–17%
  - Persistent: 25–35%
- Oligoarticular: 27–56%
- Poliarticular: 18–30%
  - RF (+): 2–7%
  - RF (−): 11–28%
- Psoriatic: 2–11%
- ERA: 3–11%
- Unidifferentiated: 10%
  - Extended: 15–20%
  - Persistent: 25–35%

JIA in Chilean cohort

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarthritis</td>
<td>35</td>
</tr>
<tr>
<td>Poliartritis FR+</td>
<td>5</td>
</tr>
<tr>
<td>Poliartritis FR-</td>
<td>10</td>
</tr>
<tr>
<td>Artritis relacionada a entesitis</td>
<td>20</td>
</tr>
<tr>
<td>Artritis psoriática</td>
<td>10</td>
</tr>
<tr>
<td>Artritis sistémica</td>
<td>10</td>
</tr>
<tr>
<td>Artritis indiferenciada</td>
<td>5</td>
</tr>
</tbody>
</table>
Clinical Characteristics

• Arthritis in juvenile SpA is predominantly peripheral (except for the hip) and usually affects lower>>upper limbs.

• Asymmetric oligoarthritis of the lower limbs is the form of the disease most prevalent at presentation, but polyarthritis occurs in up to 25% of patients at onset.

• Spine and sacroiliac joint involvement at presentation is rare but can develop 5-10 years from disease onset.

• Tarsitis is a unique characteristic of SpA.

• Enthesitis occurs in 60-80% of patients.

• Uveitis and gastrointestinal manifestations are the most common extra-articular features.

Tse S, Laxer RM. Nat Rev Rheumatol 2012.
Anatomy of arthritis and enthesitis in SpA

Tse S, Laxer RM. Nat Rev Rheumatol 2012.
## Frequency of peripheral enthesitis

<table>
<thead>
<tr>
<th></th>
<th>6 months</th>
<th>12 months</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantar fascia/calcaneus</td>
<td>20–40</td>
<td>34–64</td>
<td>54–86</td>
</tr>
<tr>
<td>Achilles tendon/calcaneus</td>
<td>11–29</td>
<td>20–50</td>
<td>34–71</td>
</tr>
<tr>
<td>Tibial tuberosity</td>
<td>0–23</td>
<td>3–29</td>
<td>7–40</td>
</tr>
<tr>
<td>Greater trochanter</td>
<td>7–11</td>
<td>7–14</td>
<td>14–32</td>
</tr>
<tr>
<td>Ischial tuberosity</td>
<td>0</td>
<td>0–6</td>
<td>0–9</td>
</tr>
<tr>
<td>Iliac crest</td>
<td>0</td>
<td>0–3</td>
<td>0–6</td>
</tr>
<tr>
<td>Tarsus, various sites</td>
<td>57–71</td>
<td>83–86</td>
<td>80–100</td>
</tr>
</tbody>
</table>

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*Table 3. Frequency (%) of peripheral entheses involved in patients with juvenile-onset SpA at different intervals*[^45][^47][^51].

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*Burgos-Vargas R. Best Pract Res Clin Rheumatol. 2002*
Spine and sacroiliac joint arthritis

- Inflammatory back pain
- Alternating buttock pain
- Schoober test
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Psoriatic arthritis

- Arthritis associated to psoriasis
- Frequent dactylitis and nail pitting.
- First-degree relatives with psoriasis.
- Can begin years before psoriasis.
- Variable joint count, usually asymmetric.
- Axial involvement usually appears in older children.
Age distribution of psoriatic arthritis

Clinical characteristics of JPsA

In favor of the splitters, not all jSpA are created equal

<table>
<thead>
<tr>
<th></th>
<th>Ankylosing spondylitis</th>
<th>Undifferentiated spondyloarthritis</th>
<th>Enthesitis related arthritis</th>
<th>Psoriatic spondyloarthritis</th>
<th>Psoriatic arthritis not related to spondyloarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroiliitis on MRI</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Sacroiliitis on X-rays</td>
<td>++++</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Inflammatory back pain</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Enthesitis (heel pain)</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Uveitis</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Crohn’s/Cölitis</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Good response to NSAIDs</td>
<td>+++</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Family history for SpA</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Elevated C reactive protein</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Previous infection</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Based on the literature and on the opinion of local experts in the care of these children.
The presence of such items excludes the undifferentiated spondyloarthritis and enthesitis related arthritis as diagnosis.

MRI = magnetic resonance imaging. NSAIDs = Non-Steroidal Antinflammatory Drugs. NA = data not available. SpA = Spondyloarthritis.
Clinical Course

- **Adult onset SpA**
  - u-SpA or axial SpA (Pre-radiographic stage)
  - Inflammatory back pain
    - Peripheral arthritis and enthesitis
  - Active sacroiliitis by MRI

- **Juvenile onset SpA**
  - u-SpA or peripheral SpA (Pre-radiographic stage)
  - Peripheral arthritis and enthesitis
    - Inflammatory back pain
  - Active sacroiliitis by MRI

- **Ankylosing spondylitis**
  - Radiographic stage

  - Inflammatory back pain
    - Peripheral arthritis and enthesitis
  - Sacroiliitis by X-rays
  - Syndesmophytes

- **Less than 5 years**
- **5 to 10 years**
- **More than 10 years**

*Burgos-Vargas R. Pediatr Rheumatol. 2012*
**Imaging in spondyloarthritis**

- Sacroiliac joint x-rays rarely show changes at diagnosis nowadays.

- MRI is most sensitive in showing bone edema, erosions and synovitis of the sacroiliac joint and spine.
  - STIR sequences are sufficient to detect bone marrow edema reflecting active inflammatory lesions.
  - Synovitis, capsulitis and enthesitis are more reliably detected on T1 post-IV gadolinium sequences.

- Ultrasound has better sensitivity than physical exam to demonstrate enthesitis but is operator-dependent.
Sacroiliac joint MRI
Labs

• Many patients with juvenile SpA have elevated platelet count, ESR and CRP, but labs can be totally normal.

• Young children can be ANA+ (particularly PsA)

• HLA B27 can determine progression to ankylosing spondylitis.
Treatment

• NSAIDs provide good symptomatic relief. Children with mild SpA could be treated only with NSAIDs.
• Sulfasalazine and methotrexate are an alternative in peripheral SpA, but are rarely effective in spondylitis.
• TNF inhibitors are the mainstay of treatment for moderate to severe cases and most cases with axial involvement.
Treatment recommendations (Go lumpers!!!)
Outcomes

- Variable disease course.
- Disease remission is reported for 17-39% of patients with jSpA and up to 44% of patients with ERA.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Outcomes in juvenile SpA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Population</td>
</tr>
</tbody>
</table>
| Minden et al. (2002)\(^{30}\) | ERA (n=33) versus JIA (n=182) | 24.0 | 16.0 | Better HAQ  
Disease remission rate in 18% (2\(^{nd}\) lowest)  
39% developed AS (mNY criteria), 36% with probable AS |
| Flato et al. (2006)\(^{39}\) | ERA (n=55) versus JIA (n=205: oligoarthritis or polyarthritis) | 85.0 | 15.3 | Worse HAQ  
Poorer physical health and increased body pain (SF-36)  
Disease remission in 44%  
35% developed AS (mNY criteria, 75% had decreased spinal mobility |
| Selvaag et al. (2005)\(^{77}\) | Juvenile SpA (n=12: 3 juvenile AS (mNY criteria), 4 SEA, 5 juvenile PsA) versus juvenile RA (n=185) | 50.0 | 3.0 | Worse CHAQ (physical function)  
Highest pain scores and patient/physician global assessment of disease |
| Oen et al. (2010)\(^{78}\) | ERA (n=36) versus JIA (n=318) | 59.0 | 0.5 | 50% ongoing active arthritis (median AJC=1)  
31% ongoing active enthesitis, inactive disease activity in 19% (2\(^{nd}\) lowest) |
| Sarma et al. (2008)\(^{79}\) | ERA (n=49) | 53.0 | 6.0 (median) | Abnormal HAQ in 75% (49% moderate to severe disability)  
62.6% ongoing active enthesitis  
Disease remission in 8%  
35% had evidence of radiologic damage (especially hips)  
65.3% experienced lost years of education  
28.6% had decreased spinal mobility |

Tse S, Laxer RM. Nat Rev Rheumatol 2012.
Conclusions

• Juvenile spondyloarthropathies are heterogenous arthritides with predominant lower limb involvement and high risk of progression to axial involvement.

• It is characterized by arthritis and enthesitis and is different from adult SpA.

• A single diagnostic or classification system that is representative of the juvenile SpA population is still needed.

• Frequently associated to HLA B27 +

• Not all juvenile psoriatic arthritis falls in the SpA group.

• As in all JIA reatment should be focused in achieving clinical remission (early use of TNFi!).
¡Muchas Gracias!