Enthesial lesions and spondylarthropathies: clinical and paleopathological insights

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Broad group of inflammatory **chronic** arthopathies or erosive arthropathies

**Spondylarthropathy (SpA)**

**Concept**: that comprises different clinical entities

Share common etiological, pathophysiological and clinical features
According to the European Spondylarthropathy Study Group (1991)

- **Ankylosing spondylitis (AS)**
  - Axial inflammation [sacroiliitis, spondylitis]
  - Peripheral arthritis
  - Enthesitis
  - Eye and mucocutaneous lesions
  - Genetic features
  - Association with *HLA-B27* antigen

- **Psoriatic arthritis (PsA)**
  - Arthritis associated with psoriasis

- **Reactive arthritis (ReA)**
  - Arthritis consequence of extra-articular infection - generally genitourinary and/or gastrointestinal

- **Undifferentiated spondyloarthritis (uSpA)**
  - Clinical spectrum does not correspond to any other entity

- **Juvenile SpA**

- **Enteropathic arthritis (EA)**
  - Arthritis connected with inflammatory bowel disease

- **SAPHO- ?**
**Between entities:** overlap of symptoms and signs

**Each entity:** heterogeneity of disease phenotype
Spondylarthropathies

General prevalence: 0.5% - 2%

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Prevalence</th>
<th>Sex</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankylosing spondylitis (AS)</td>
<td>0.2-1.2%</td>
<td>M&gt;F</td>
<td>20-30</td>
</tr>
<tr>
<td>Reactive arthritis (ReA)</td>
<td>0.1%</td>
<td>M&gt;F</td>
<td>20-35</td>
</tr>
<tr>
<td>Psoriatic arthritis (PsA)</td>
<td>0.1-1%</td>
<td>M=F</td>
<td>40-50</td>
</tr>
<tr>
<td>Enteropathic arthritis (EA)</td>
<td>0.2%</td>
<td>M=F</td>
<td>20-30</td>
</tr>
<tr>
<td>Undifferentiated spondyloarthritis (uSpA)</td>
<td>0.7-2%</td>
<td>F&gt;M</td>
<td>20-30</td>
</tr>
</tbody>
</table>

Haida Indians, Canada: 4.2% AS
Navajo (USA), Pawaia Papua New Guinea,
Alaska Natives, Chukotka Russia
Interaction

- Immune system
  - HLA-B27 allele

- Environmental stimuli
  - Bacterial pathogens
  - Mechanical stress
The abnormal **inflammatory response** characterizes these conditions:

**Enthesitis** and **synovitis** are the fundamental pathological characteristics in SpA

The inflammation occurs primarily at the enthesis or at the synovium?
I- Primarily enthesial disease

• Postulated during the 70's  Ball and co-workers: First description of inflammation at the enthesis on SpA

• Reviewed by Fourier et al. (2004): “enthesal territory” - Broaden the concept of “entheses” to include the amphiarthroses and diartho-amphiarthroses

  main and initial target of the disease process in SpA

• McGonagle & Benjamin research group: “enthesis organ”

Primary event: Enthesitis (fibrocartilaginous enthesis)

Secondary spread of inflammation to the synovium
II - The synovium

• Other lines of research: inflammatory process of the joints cannot be explained by enthesitis alone.

[François et al., 2000; François et al., 2001; Lories et al., 2004; Helliwell & Porter, 2007]

III - The bone

• Other lines of research: crucial role of bone marrow inflammation, as initial process in SpA. Autoimmunity is at the core of this proposal

[Jacques et al., 2008]
Pathological features

Spondyloarthropathies

Key features:

**Enthesis** [Fibrocartilaginous] -- Synovial joints -- Cartilaginous joints

- Articular
- Extra-articular

Distinctive characteristic:

- Erosions
- New bone formation
- Ankylosis

SKELETON: Axial and appendicular
Pattern of distribution

Spondylarthropathies

ARTICULAR LESIONS

AXIAL

• Sacroiliac (SI)
• Vertebral body
• Zygaphyseal
• Costovertebral
• Pubic symphysis
• Manubriosternal
• Acromioclavicular
• Sternocostoclavicular

APPENDICULAR

• Hands and feet
• Shoulder
• Hip
• Knee
Spondylarthropathies

- Sacroiliac Joint (SI)

**Paleopathological features**

ISCMB, SI Joint

ISCMB. SI Joint
Spondylarthropathies

Paleopathological features

- Column: vertebral body

Syndesmophytes: thin, marginal, vertical growths - Inflammation on the insertion of the outer fibers of the *anulus fibrosus* and short fibers of the *anterior longitudinal ligament*. [Entesophytes]

From: Freemont (2002) pg. 5 - Syndesmophyte formation.
Spondylarthropathies

• Column: vertebral body

Parasyndesmophytes (paramarginal ossification, paravertebral ossification)

Bulky growths, non marginal - ossification of the structural ligaments of the spine and of the insertion on the circumferential area the body.

SpA: Asymmetrical, aleatory
Spondyloarthropathies

Paleopathological features

• Column: posterior region

Lesions
• Zygapophyseal joint
• Costovertebral joint
• Spinous process
Spondylarthropathies

Paleopathological features

ISCMB. Bamboo spine
Spondylarthropathies

- Appendicular skeleton: peripheral joints
Spondylarthropathies

- Appendicular skeleton

- Scapula
- Humerus
- Radius
- Knee Joint
Spondyloarthropathies

Pattern of distribution

**Articular Lesions**
- Iliac crests
- Ischial tuberosities
- Vertebral spinous processes
- Calcaneus [Achilles tendon and plantar fascia]

**Classic Entheses**
- Ligaments of hand and feet
- Patella
- Tibial tubercle
- Greater lesser trochanters
- Shoulder
- Humeral epicondyles
- Ulna (olecranon)
In SpA, the lesions at entheses are important features.

The scrutiny of these conditions should be performed when analyzing enthesophytes on the research of human activity patterns.

How attainable is to identify SpA in paleopathology?
Hypothesis: Methodological impact on the assessment of spondylarthropathies in past populations

Based on previous paleopathology data

- Considered rare
- Variation of the diagnostic criteria used
- Scarce population approach to SpA
- Existent studies present accentuated range of disease prevalence
**Identified Skeletal Collection Museu Bocage**

*Museu Nacional de História Natural, Lisboa*

\[N = 573\] adults [Age range: 20-98 years old]

- \[N = 314\]♀ [55%]
- \[N = 259\]♂ [45%]

**Biographical data**

- **Sex**
- **Age at death**
- **Year and cause of death**
- **Place of birth**
- **Occupation**

**Chronology:** 19th-20th centuries
Lesions analysis

• Macroscopic observation

Methodological Test

• Diagnostic criteria described on the works of:
  • Martin-Dupont (2005)
  • Rogers e Waldron (1995), Rogers et al. (1987)

Equal
• Sample
• Observer
• Observation parameters
Spondylarthropathies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroiliac [N=496]</td>
<td>1.8%</td>
<td>9</td>
</tr>
<tr>
<td>Zygapophysis [N=514]</td>
<td>9.9%</td>
<td>51</td>
</tr>
<tr>
<td>Syndesmophytes [N=514]</td>
<td>10.7%</td>
<td>55</td>
</tr>
<tr>
<td>Paravertebral [N=514]</td>
<td>5.1%</td>
<td>26</td>
</tr>
<tr>
<td>Lesion peripheral joints [N=510]</td>
<td>3.7%</td>
<td>19</td>
</tr>
<tr>
<td>Fusion peripheral joints [N=510]</td>
<td>1.2%</td>
<td>6</td>
</tr>
</tbody>
</table>
Spondylarthropathies

Results & Discussion

- No association [isolated lesion]
- With association [association with at least one other SpA feature]

<table>
<thead>
<tr>
<th>Condition</th>
<th>No association</th>
<th>With association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacroiliac</td>
<td>7 (77.8%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>Zygapophysis</td>
<td>30 (58.8%)</td>
<td>21 (41.2%)</td>
</tr>
<tr>
<td>Syndesmophytes</td>
<td>37 (67.3%)</td>
<td>18 (32.7%)</td>
</tr>
<tr>
<td>Paravertebral</td>
<td>20 (76.9%)</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Lesion peripheral joints</td>
<td>16 (84.2%)</td>
<td>3 (15.8%)</td>
</tr>
<tr>
<td>Fusion peripheral joints</td>
<td>2 (33.3%)</td>
<td>4 (66.7%)</td>
</tr>
</tbody>
</table>
This results confirmed that:

- The most “typical” and complete pattern was infrequent
Results & Discussion

Spondylarthropathies

- Rogers e Col. Martin Dupont (2005)
- Rothschild e Col.

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>3.9%</td>
</tr>
<tr>
<td>B</td>
<td>10.7%</td>
</tr>
<tr>
<td>C</td>
<td>15.6%</td>
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</tbody>
</table>

- Group A: n=20
- Group B: n=55
- Group C: n=80
### Spondylarthropathies

<table>
<thead>
<tr>
<th>Clinical Report</th>
<th>Lesion</th>
<th>Clinical diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erb et al. (2005)</td>
<td>Sacroiliitis</td>
<td>Lupus, sarcoidosis, infectious disease</td>
</tr>
<tr>
<td>Braun &amp; Sieper (1996)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hoshino et al. (2006)</td>
<td>Sacroiliitis</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>Rombauts et al. (2000)</td>
<td>Zygapophyseal ankylosis</td>
<td>Septic Arthritis</td>
</tr>
<tr>
<td>Van Offel et al. (1995)</td>
<td>Sacroiliac ankylosis, zygapophyseal ankylosis (intra-articular), erosive arthritis with bone formation on hand and feet</td>
<td>Ochronosis</td>
</tr>
<tr>
<td>Canhão et al. (1996)</td>
<td>Bambu spine, sacroiliac and zygapophyseal ankylosis, hand and feet arthritis</td>
<td>Ochronosis</td>
</tr>
<tr>
<td>Fiske et al. (1995)</td>
<td>Bambu spine, sacroiliac ankylosis</td>
<td>Paralisys secondary to amyotrophic lateral sclerosis</td>
</tr>
</tbody>
</table>

Additionally, *Calcium pyrophosphate deposition disease* (CPDD) is clinically evoked as a differential diagnosis.
Results & Discussion

Spondylarthropathies

Sample by the method of Rogers & col
N= 20
Mean age at death= 75 years old

<table>
<thead>
<tr>
<th>Entesopathy</th>
<th>% (N=20)</th>
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</thead>
<tbody>
<tr>
<td>Iliac crests</td>
<td>58%</td>
</tr>
<tr>
<td>Ischial tuberosities</td>
<td>44%</td>
</tr>
<tr>
<td>Calcaneus [Achilles tendon and plantar fascia]</td>
<td>44%</td>
</tr>
<tr>
<td>Patella</td>
<td>42%</td>
</tr>
<tr>
<td>Tibia [anterior tuberosity]</td>
<td>21%</td>
</tr>
<tr>
<td>Femur [greater and lesser trochanters]</td>
<td>42%</td>
</tr>
<tr>
<td>Humeral head</td>
<td>47%</td>
</tr>
<tr>
<td>Humeral lateral and medial epicondyles</td>
<td>15%</td>
</tr>
<tr>
<td>Ulna [olecranon]</td>
<td>35%</td>
</tr>
</tbody>
</table>
Spondylarthropathies

ISCMB. Calcaneus

ISCMB. Calcaneus

ISCMB. Iliac crest
Results & Discussion

Spondylarthropathies

ISCMB. Humeral head

ISCMB. Ulna
Clinical Data

- Reduced assessment of occurrence of peripheral entheses - under diagnosed

- Generally co-exists with other clinical manifestations of SpA, but isolated occurrence was reported by D’Agostino & Olivieri (2006): 14% of individuals with juvenile-onset disease and 9% with late-onset

- Peripheral enthesitis: observed in all forms of SpA and all phases (D’Agostino & Olivieri, 2006)

- Entesopathy of the calcaneus: one of the most frequent and early sign

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<td>Ankylosing spondylitis (AS)</td>
<td>25-58%</td>
<td>78.3%</td>
</tr>
<tr>
<td>Reactive arthritis (ReA)</td>
<td>33–58%</td>
<td>93%</td>
</tr>
<tr>
<td>Psoriatic arthritis (PsA)</td>
<td>20%</td>
<td>-</td>
</tr>
<tr>
<td>Enteropathic arthritis (EA)</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>PsA+ EA+ USpA</td>
<td></td>
<td>82.4%</td>
</tr>
</tbody>
</table>
Spondyloarthropathies

Even if SpA diagnosis is problematic - methodological controversy

Each of the mentioned lesions

• Sacroiliac or zygapophyseal joints: erosion/ new bone formation or intra-articular ankylosis

• Syndesmophytes

• Presence of paramarginal (paravertebral) ossifications

• Erosive lesions with bone proliferation or intra-articular ankylosis on the peripheral joints

Relevant Signs

To be considered on the evaluation of enthesophytes as activity marker
• Methodological impact on the assessment of SpA: limits population comparison without taking into consideration the diagnostic criteria applied

• Further research on the variability of the morphology of lesion is required

• Improvement of differential diagnosis

• Enthesitis is key feature of SpA: although the more distinctive are the ones of the axial skeleton

• The recognition of the SpA is important on the analysis of markers of activity
Acknowledgments

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